COLD INJURY

Transactions of the Fourth Conference
November 7, 8, and 9, 1955, Princeton, N J

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Fourth Conference on Cold Injury

THE JOSIAH MACY, JR FOUNDATION CONFERENCE PROGRAM

DURING THE PAST FIFTEEN YEARS the Josiah Macy Jr Foundation has organized more than twenty conference groups each group meeting for at least two days annually over a period of five or more years Each meeting is limited to twenty five participants (members and guests) selected to represent a multidiscipline approach to some urgent problem in the field of medicine and health The goal of this conference program is the promotion of communication the exchange of ideas and the stimulation of creativity among the participants The publication of the Transactions of the meeting is undertaken to share as far as possible the conference process with a larger audience than could participate personally in the discussions

These conferences provide an opportunity for informal give and take among the participants To further this purpose the number of presentations planned for each day is generally restricted to one or two The member or guest selected to give such a presentation is requested not to read a paper but rather to highlight in an informal manner some of the more interesting aspects of his or her research with the expectation that there will be frequent interruptions by participants in the form of questions criticism or comment Such interruptions during the course of a presentation are encouraged and form an essential part of the group interchange

The conference program has always been viewed by the Foundation as an experiment in communication in which there is room for improvement and need for frequent reappraisal Sufficient experience has already been gained to justify the conclusion that this type of conference is an effective way of improving understanding among scientists in medicine and allied disciplines of broadening perspectives of changing attitudes and of overcoming prejudices The further conclusion has been reached as the result of this experiment that the major obstructions to understanding among scientists lie in the resistance of human attitudes to change rather than in difficulties of technical comprehension Less extensive experience with non scientists has indicated that the effectiveness of this type of conference is not limited to groups of scientists

but will function in any group meeting where more effective communication is the primary goal It is also clear that the same conference technique with minor changes is readily adapted to small international conferences

The style of publication of the Transactions has aroused considerable interest and some criticism The criticism has been directed primarily to editorial permissiveness which has allowed in the final test in some instances too many questions remarks or comments which although perhaps useful during a heated discussion seem out of context and interrupt the sequence of thought in the printed volume A few have objected to the principle of publishing in this style and would prefer a depersonalized summary without interruptions

The Foundation Staff and the Scientific Editors of these volumes welcome criticism and hope to profit thereby in increasing the usefulness of the Transactions to scientists and students of science in this country and abroad

FRANK FREMONT SMITH M D
Medical Director

FOLLOW-UP STUDY OF COLD INJURY CASES FROM THE KOREAN WAR*

JOSEPH R. BLAIR
Army Medical Research Laboratory
Fort Knox, Ky

THOSE OF YOU WHO WERE PRESENT at the second conference in New York will recall that Lt Col Kenneth D Orr and Comdr Leonard M Schuman (1) gave a very complete coverage of the epidemiology and the acute phases of cold injury as it was observed in Korea A group of us at Harvard Medical School in Boston, through contracts with the Army Medical Service,* have continued these studies originally begun by Colonel Orr (2) and have just completed a follow up study on these cases 4 years after injury

The 100 cases on which we are going to present some data for your consideration and discussion are fairly representative of the approximately 5600 cases of cold injury that were evacuated from Korea during the winter of 1950 51 We were very fortunate that in these 100 cases we had very complete records, i e, histories, physicals physiologic measurements, photographs, laboratory studies, and roentgenograms, from shortly after occurrence of cold injury right on through channels of evacuation periods of hospitalization, rehabilitation and return to military duty or civilian life The original study, in most cases, was carried out over a period of about 18 months Since then these patients had not been restudied until our group at Harvard Medical School had the opportunity of doing so

Table I reveals the degree of success we enjoyed in our follow up study of the original 100 frostbite cases Through the services of the Army Adjutant General and the Veterans Administration we were able to locate all 100 of these former patients Letters were written requesting their voluntary participation in the follow-up study completion of history forms and frostbite questionnaires,

*The work here reported was supported by Contract DA49 007 MD-342 between Harvard University and the Office of the Surgeon General Department of the Army

The medical histories clinical summaries physiologic data serial photographs and serial roentgenograms used in this study have been indexed and filed in the library of the Army Medical Research Laboratory Fort Knox, Kentucky and are available to any interested students or investigators

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The m l c l l stor e cl n cal sum nar es phys ol g c d ta serial photographs and seri l roentg nograms use l n th s study have been ind xed and filed in the ll r r f tl Army M d l R se r h Laboratory Fort Knox Kent cky and are l l l to an nter ted st dents or in est g tors

and that they report to Army and Veterans Administration hospitals for physical examination, photographs, and roentgenograms Ninety-seven of the 100 patients volunteered to participate in the study Three did not reply although it was established that our letters were received Of the 97 who returned the completed questionnaires and histories, 89 actually reported to medical installations for physical examination, roentgenograms, and photographs We were fortunate in being able to conduct personally the physical examinations and various studies on fifty of these patients This number was limited by the fact that many of the patients lived in Hawaii and Puerto Rico, or were still in the Armed Forces on various overseas assignments

TABLE I

Summary of Follow-Up Study of Cold Injury Patients 4 Years After Injury

No patients in study	100
No patients located	100
No patients participating (answering mail questionnaires)	97
No patients x rayed	89
No physical examinations (by the authors)	50

The study was carried out by the following procedures Our group drew up a set of history forms and frostbite questionnaires that were sent to the patients to be completed and returned One question that has disturbed us greatly and to which we do not have a final answer is, how valid is the information derived from these questionnaires? Interpretation of the data must be made in light of two facts (1) the frostbite questionnaires were completed by patients with no supervision or instructions other than that in the cover letter, and (2) approximately one-third of the patients are drawing disability compensation from the Veterans Administration which they are very anxious to protect and not give answers that may jeopardize it

We have used three methods in trying to increase the accuracy of answers on the questionnaire (1) We have placed in the questionnaires many questions asking the same thing but in different phraseology as a cross check on the answers received (2) When a questionnaire was returned with answers which did not agree with the severity of injury previous history or physical examination a second and sometimes third questionnaire was sent to these individuals at intervals of several months The various questionnaires were then cross examined for accuracy and consistency of information supplied. (3) When we personally examined the fifty study patients the questionnaires were checked very carefully against physical examinations and medical histories These procedures have greatly increased the accuracy of the data from the questionnaires but the symptoms are still not consistent with organic physical findings The symptoms are much more severe than organic lesions would indicate

Table II gives some knowledge of the background and characteristics of the study group The majority or 85 were young males from 17 to 25 years of age They were about evenly distributed between whites and Negroes with two Puerto Ricans one Japanese American and one Hawaiian in the group They were all enlisted personnel primarily in the three lower grades

As to the site of the frostbite lesion in these 100 cases Table III shows that it occurred in one or both feet in a total of 97 patients The hand was frostbitten in 11 patients and in some cases both hands and feet were involved This is about the same ratio observed in the 5600 patients evacuated from Korea approximately 3 per cent had hand involvement only 10 per cent had hands involved with or without the feet and 97 per cent had involvement of feet

As to the severity of the lesion 69 or over two thirds of the group had a third degree cold injury second degree 10 and fourth degree 19

We have still another classification the so-called ill defined condition of the feet * This is a diagnosis for a foot condition that occurred frequently in Korea but which could not be established as a true frostbite lesion First the lesion was not localized as was the typical frostbite lesion and secondly it occurred frequently at

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TABLE II

Distribution of Patients as to Age, Race, and Rank

Age		Race		Rank	
Years	No	Race	No	Grade	No
17 to 20	53	White	55	Pvt	35
21 to 25	32	Negro	41	Pfc	37
26 to 30	7	Puerto Rican	2	Cpl	22
31 to 35	6	Japanese American	1	Sgt	5
36 to 40	2	Hawaiian	1	Sfc	1

TABLE III

Site and Severity of Cold Injury Lesions

Site of Lesion	Frostbite			Ill Defined Condition of the Feet	Total
	2	3	4		
One foot	3	18	0	0	21
Both feet	4	47	15	2	68
Hands	0	0	3	—	3
Hands and feet	3	4	1	—	8
Total	10	69	19	2	100

temperatures well above freezing It was characterized by erythema hyperhidrosis and maceration and it appeared quite similar to mild trench foot but there was no numbness or hypesthesia

Incidence of ill defined condition of the feet was a little higher in Korea than in our study group about 10 per cent or roughly 500 of the 5600 cases were diagnosed as "ill defined condition of the feet Only two of our 100 study patients had such a diagnosis

Tremont Smith Did those who had genuine frostbite in one area of the extremity ever have the equivalent of "the ill defined

condition in surrounding areas? In other words did you ever find two or three other toes with what you called an "ill defined condition of the feet if you did not find a genuine frostbite in one toe?

Blair Yes when there was a severe frostbite in say the large toes occasionally in the adjacent toes there existed a condition quite similar to our so called ill defined condition However it is only when such a condition of erythema and maceration involves much of the foot without the presence of true frostbite that we diagnose it as ill defined condition of the feet

Personally I cannot say whether "ill defined condition of the feet is or is not mild trench foot

Fremont Smith I saw quite a number of men from the Battle of the Bulge at the Brooks General Hospital and some of them showed just the condition that you described it seemed to me that this was also present in many that had actually lost toes or lost tissue in the surrounding area

Blair I have seen a number of color transparencies at the Armed Forces Institute of Pathology showing these lesions you speak of and they were diagnosed originally as mild trench foot In appearance they look quite similar to this ill defined condition of the feet

Fremont Smith The ill defined condition might be in one foot and the other foot might have a loss of two or three toes

Blair Possibly yes As a rule however it was bilateral in most cases and quite diffuse without any severe frostbite lesion being present

Talbott Was the temporary incapacity in those with "the ill defined condition" sometimes more severe than a localized first degree or maybe even a localized second degree frostbite?

Blair Yes From the standpoint of the impairment of function a fairly severe ill defined condition of the feet" bilaterally was more severe than localized first degree frostbite

Fremont Smith It was quite striking at the Brooks General Hospital that those who had lost no tissue in many instances were far more incapacitated than those who had lost a toe Of course the question of return to duty seemed to play a role to some extent in these cases The one who had lost a toe knew he was not going back to duty

There was one man with very marked cyanosis of both feet but no loss of tissue a striking example of this ill defined condition

He had been incapacitated and he was asked how far he could walk now (He had been recovering for several months and said he could walk about a quarter of a mile without too much trouble) The Acting Inspector General of the Army, General Snyder, said to him, "Well, I guess you are about ready to go over and join General MacArthur, aren't you?

I happened to look down at this man's feet just at that moment — feet which were cyanotic, and all of a sudden those feet blanched to a dead white I have never seen a more striking shutdown of circulation I called General Snyder's attention to it immediately It was an example of Raynaud's phenomenon right in front of our eyes, and precipitated by this situation Yet there was nothing in the man's face that showed any indication of what I attribute to be the rage that he was feeling at the idea that he, after he had done his bit, would now be sent back to duty, this rage was expressed only in the vasoconstriction of his feet

I have always had the feeling that there developed a hyper reactivity of blood vessels and sweat glands, as the result of genuine but mild cold injury and this hyperreactivity was then kept going in part by such reactions as this I should add that General Snyder very quickly reassured him and his feet very quickly resumed their previous cyanotic color

Shumacker Is it not true, Colonel Blair, that your summary excludes many cases of soldiers who thought they had sustained a cold injury but in whom nothing was demonstrable once they had been placed in a warm environment? By and large they were returned quickly to duty and they were not diagnosed as having sustained a cold injury .

Blair That was true, Dr Shumacker, in Korea Fortunately, the symptoms of most of those men, once they came into a warm room, disappeared, and as a result, very few of them appeared among the 5600 patients evacuated from Korea Therefore, it is almost impossible to hazard a guess as to how many actual cold injuries occurred in Korea Most of us would prefer to speak in terms of the 5600 cases evacuated from Korea, without making any wild guess as to those that had very mild first degree injury and those that returned to duty after coming into a warm room for a short period

We know from experience that there are probably more cases of first degree cold injury than there are of second, third, and fourth degrees combined But in the statistics of those evacuated from

Korea, first degree is the smallest number only because they were by far the smallest percentage evacuated

Horvath Is that because you insist that the diagnosis of frostbite or cold injury is a visible, actual destruction of tissues?

Blair No, I do not think so I believe the reason is simply that a person has to be severely injured before he is evacuated from a theater, and the low percentage is merely a result of the sorting out of patients for evacuation

Of course, there is always the question, when do you make the diagnosis of cold injury? That is quite a problem When there is at least second degree injury, it is easy to make the diagnosis but when a patient comes in with a much less severe injury it becomes quite difficult to decide whether or not it is first degree frostbite

Talbott And a number of men had first degree injury who were quite sturdy souls They did not report in and went back to duty, probably never getting on any list of statistics

Blair That is true, and in going through the histories it is evident that in almost every case the man said he had been out a month or longer with cold feet and blisters, and it was only after it occurred a second or third time, or after his feet became so sore that he could not walk, that he reported in to an aid station

Montgomery Colonel Blair, would you differentiate for us between the "ill-defined condition of the feet" and trench foot?

Blair Let me talk a little about the nomenclature of "ill-defined condition of the feet" First of all, in the soldiers evacuated from the Chosen Reservoir, frostbite was easily diagnosed, it was unquestionably cold injury Later, men were evacuated with foot lesions which were quite diffuse, erythematous some swelling, markedly hyperhidrotic and macerated In the Korean theater those lesions were not considered to be frostbite because of the nature of the lesion, its distribution, and also because it occurred in above freezing temperatures The condition may have developed over a period of days instead of being an acute episode as is the case in most frostbite

Montgomery But it was primarily because tissue was not lost that they were not defined as frostbite?

Blair Or because there was no localized lesion but a quite diffuse one They appeared to be quite similar to the color transparencies of very mild trench foot of which I previously spoke It was established in the nomenclature that these nonfrostbite foot

injuries would be diagnosed as ill defined condition of the feet I could not say that they were or were not a mild degree of trench foot The conditions in Korea were ideal for producing trench foot The men were pinned down in rice paddies and temperatures were near or just above freezing The lesions developed over a long period of time and could very well have been a mild trench foot

Montgomery Then the ill defined condition includes trench foot?

Blair It would include any trench foot that occurred in Korea because there was no diagnosis made *per se* of trench foot in Korea Such foot lesions as described were diagnosed as either frostbite or ill defined condition of the feet We certainly did not see any trench foot lesions as occurred in the Battle of the Bulge the Aleutians or Italy

Shumacker I would certainly agree I did not see anything in Korea or Japan that resembled the trench foot of World War II as far as its origin and clinical manifestations were concerned Isn t it true also that some individuals who did not necessarily have cold feet but had worn shoepacks for a long period of time also developed a condition quite like the one to which you are now referring?

Blair It is quite true that some individuals developed water logged and macerated feet because they wore shoepacks for days at a time without changing their socks A superimposed cracking of the skin and secondary infection were often seen

Crismon The lesions turned up after the introduction of the double insulated boot a boot where there was no breach of continuity of the insulation

Shumacker I think that is right You will recall that one of the Naval officers assigned to the Cold Injury Study Team traveled around a great deal up at the front and took a roundabout way of getting back to his post He developed this condition and he stated that his feet really were not cold at all It was a question of having had on these insulated boots with wet feet for a long period

Horvath But you can get the same thing without the shoepacks on having the feet exposed to the cold I think Captain Behnke and I had that experience

Hedblom Doesn t this ill defined condition of the feet predispose to further injury in a lesser degree of cold and over a lesser period of time?

Shumacker I think so

Blair I also think so I am unable to give any specific instances of that occurring but I often wonder if such a condition as this might not predispose an individual to a more severe cold injury

Hedblom The reason I am very concerned is because this boot is one of the items issued to all hands on the coming Antarctic Expedition with the assurance that these will keep feet in tiptop shape I do not believe it

Blair You are right Captain Hedblom because the insulated boot is not the cure all or the answer to all foot problems in the Army the Navy the Marines or any branch of the service The discipline and training in the use of the insulated boot are probably more important than in any other type of footwear we have ever had One must maintain a rigid discipline of foot care of foot drying of changing of socks and cleanliness more so than in any footwear we have ever developed True the insulated boot does give much better protection against low ambient temperatures but it is not the cure all for all foot troubles in the Armed Forces When properly used the insulated boot can be a major advance in protection against cold injury

Horvath It certainly is true that with proper foot care less adequate insulation kept people from getting frostbitten We had plenty of experience with that during the last war

Simeone Colonel Blair did you say that most of these Korean casualties had been exposed to actual freezing weather?

Blair Table IV will answer that question It shows the exposure conditions under which these individuals suffered their cold injury The ambient temperatures on the left show that the vast majority of them experienced their cold injury in the range of 1° to 20°F At the very low temperatures the numbers may be deceiving They do not indicate that a person is less likely to get injured at the lower ambient temperatures but merely the fact that we had only 2 days during which the temperature dropped below −20°F whereas higher temperature days were extremely numerous If the cold injury were expressed as a cases per day rate it might be clearer

As to exposure time this bears out Dr Shumacker s statement of a moment ago that he did not see anything in the etiology of cold injury that resembled what he observed in Europe in World War II the vast majority of cases occurred after an exposure period in the cold of from 7 to 12 hours which is a much shorter exposure time than that of the vast majority of trench foot cases of World

TABLE IV

Cold Injury in Relation to Ambient Temperature (°F) and Hours of Exposure

Temperature		Exposure Time	
Temp (°F)	No Cases	Hours	No Cases
Above 20	11	0 to 6	16
1 to 20	65	7 to 12	62
–20 to 0	14	13 to 18	12
Below –20	10	Above 18	10

War II Those cases with exposure periods above that, the 13 to 18-hour and above 18-hour groups, were usually quite severely frostbitten, but interestingly enough, most of the "ill-defined conditions of the feet" were in men that were exposed for a long period of time at temperatures above 20°F They would, therefore, fall into the long exposed group Does that answer your question?

Simeone Yes, I wonder, too, if that is representative of the Korean experience or simply representative of these 100 cases that you studied

Blair This is quite representative of the Korean situation because this group of 100 cases, with a few minor exceptions, were selected to represent the general Korean cold injury picture About two thirds of the cold injuries in Korea occurred in the 1° to 20°F range, and about 60 per cent of the cases gave a history of from 7 to 12 hours exposure in the cold However, some received their cold injuries in a much shorter period of time, Colonel Orr's report shows that some suffered injury in as short a period as 2 hours and others were exposed as long as 72 hours, these being the extremes

Simeone That is an important distinction between the Korean group and the World War II group because in the latter I would say that certainly a very large proportion of them were exposed for 2 or 3 days, on the average, and in above-freezing weather, as a rule

Talbott That means that part of the definition, then, of trench foot is the environment of the foot in which there is damage

Simeone Yes, it is a slower process

Talbott The segregation of the cases in the Korean conflict was based in part upon Colonel Orr's arbitrary definition, which centered about his experience, to be sure but I think that you are following

his definition quite closely He was the one who saw more of the cases than anyone else and had greater responsibility clinically for the bulk of the 5000 odd cases than anyone else

Blair That is correct

Talbott He was under the impression that most of these cases were frostbite because of the freezing or subfreezing temperature in the environment

Blair Together with the short periods of exposure

Behnke You have defined the ill defined Now can you define he well defined ?

Blair We had an earlier discussion of this European workers ve classified cold injury into three degrees first second and rd First degree consists of erythema and swelling with no blister mation There is a reddened skin similar to moderate sunburn mild first degree burn Second degree is one of bleb or blister ation which of course gives the possibility of an open lesion as distinct from first degree Third degree is one of gangrene or tissue necrosis without any further breakdown as to amount or degree of tissue necrosis

The above is a little more easily defined classification than that of breaking frostbite down into four degrees However Colonel Orr clinically used the Russian classification which divides cold injury into four degrees It is certainly more helpful clinically in the management of cold injury to be able to classify it into four degrees rather than three In such a classification the third degree group is broken down into two groups third and fourth Third degree is full skin thickness injury gangrene but not severe enough to cause loss of a part Fourth degree is complete necrosis and loss of a part A patient with third degree cold injury can often be kept in the Communication Zone treated rehabilitated and possibly returned to duty but a patient with fourth degree injury is one that must be returned to the Zone of Interior to undergo extensive surgery rehabilitation and finally disability discharge or return to military duty For this reason it is very helpful to classify cold injury as first second third and fourth degrees third and fourth degrees being injuries with tissue necrosis No tissue necrosis occurs in first and second degree cold injury

Behnke The exact diagnosis then is made later isn t it?

Blair The diagnosis is attempted early but only confirmed late It is very difficult to determine early and accurately the degree of injury The diagnosis is not too difficult of first second and third

degree frostbite, but to distinguish early between third and minimal fourth degree frostbite is extremely difficult

Fuhrman Can you establish in what percentage of these cases actual freezing did occur?

Blair That is a question that I can answer in a general way only, meaning that icing of the tissues which I believe you are referring to occurred in a good number of cases However, by the time the first medic had seen and examined them, thawing had occurred in the vast majority Colonel Orr reported that only 2 per cent of all cases were still in an iced condition when first seen by medics

Fuhrman But more had been in an iced condition

Blair From the histories that the patients give, a much larger percentage than 2 per cent were definitely in an iced condition But I daresay that no one could even hazard an accurate guess as to the correct number

Montgomery Is that 2 per cent of the third and fourth degree groups?

Blair That is 2 per cent of all cases of frostbite

Fuhrman Could you make an intelligent guess as to the rough average time that the ice was present in the tissues?

Blair I could not even make an intelligent guess at that, Dr Fuhrman

Shumacker Colonel Blair from my very brief visit there, I would certainly agree with you I do not think it is possible to give the answer From talking to and examining men who were evacuated to Taegu or Osaka or were seen shortly after injury near the front I was certainly impressed with the fact that only in a small per centage was there any evidence with suggested icing of tissues My guess would be that this occurred in more than two but still in a relatively small percentage of cases

Blair I agree with you on that, Dr Shumacker, it occurred in the minority of cases It was higher than the 2 per cent we show here but my guess would be that it was certainly less than 20 per cent

Fuhrman But you are still using the term 'frostbite for these acute injuries?

Blair Yes We are using the term 'frostbite' possibly incorrectly if you define "frostbite' as a lesion produced only by icing of tissues Rather we are using 'frostbite" in contrast to what Dr Simeone and Dr Shumacker described as the immersion foot syn-

drome Our frostbite" lesion occurs at sub-freezing temperatures and over a relatively brief period of exposure

Sweet Colonel Blair, while you are defining things, what is a shoepack?

Blair During World War II we had a footgear which was half rubber and half leather, meaning that the lower part of the footwear was rubber and impervious to any moisture or water, either from the inside or out, that is it blocked perspiration from getting out and water from coming in This lower portion was bound to an upper part of leather which was laced about the foot

It was usually worn with a pair of felt insoles, a cushion sole sock and usually one ski sock That was our commonly used cold wet footwear and was issued to troops in Europe and the Aleutians

The other footwear that Dr Shumacker and Dr Crismon spoke of is an all rubber sealed insulation boot that was issued for the second winter in Korea The insulation that is normally provided by socks and felt insoles is sealed in between two layers of rubber on the theory that if the insulation remains dry then it will retain its full insulating property This footwear is normally worn with only one pair of cushion sole socks It is certainly a better protective device against low ambient temperatures than the shoepack but it requires considerable care in its use because all the perspiration from the feet is collected within the footwear Even though the foot may stay warm, a water-soaked foot with considerable maceration and denudation can result

Schatzki Is that completely insulated on top?

Blair It is insulated all the way up to the top It is open partially at the top where the laces tie and some moisture can come out through the top of the boot

Burton Perhaps I should make one minor point Colonel Blair mentioned that the shoepack had an all rubber bottom and leather top It is important to realize that the all leather top is quite impermeable to water vapor In essence, it is the same, physiologically as if it were all rubber The leather is treated in such a way that it does not let water vapor through in distinction to the mukluk for instance, which the Eskimos wear which is quite permeable to water vapor

It is a minor point but I think you should not give the impression that the shoepack has impermeability only on the bottom

Blair Yes I am glad you brought that up because I did not intend to create that impression

Simeone In keeping with Dr Burton s remarks the maceration of the skin of the feet was a considerable problem with the shoe pack as well as with the insulated boot when the temperature was above freezing

Blair There was one little advantage with the shoepack in that in addition to the cushion sole sock a pair of felt insoles and a ski sock helped to soak up some of the water so that the man was not walking quite so much in his own perspiration as in the insulated boot

As to what has happened to these individuals 4 years after their cold injury in Table V we have listed on the left the degrees of injury and then the number of patients in each category We note that in all degrees of injury there are some who received disability discharges But as you would expect the more severe the injury the greater the number of disability discharges and percentage of disability allowed

TABLE V

Disability and Employment Status of Patients 4 Years After Cold Injury

Cold Injury		Disability Discharge		Employed		Handicapped	
Degree	No Pts	Yes	No	Yes	No	Yes	No
Second	10	2	8	10	0	5	5
Third	67	18	49	63	4	37	30
Fourth	18	16	2	16	2	12	6
I D C F *	2	1	1	2	0	2	0
Total	97	37	60	91	6	56	41

* Ill defined condition of the feet

In fourth degree injury involving 15 cases of feet and three cases of hand injury all or 100 per cent received disability discharges The two that are listed as No did not get disability discharges because they are still on active duty in the Army but they have been rated for allowable disability by the Veterans Administration at any time that they should leave the service So actually all fourth degree cases rate disability discharges

Ninety one of the 97 former patients are gainfully employed but more than half of them complain that either in obtaining employment or in carrying out their particular job they are handicapped by their previous cold injury One thing that would lead us to be somewhat suspicious of the questionnaire method is the fact that with second and third degree injury more than half claim that they have difficulty in carrying on with their job

As to the actual complaints that these individuals made the symptomatology will be shown by Table VI which shows the six most common complaints or symptoms that we found among these former soldiers 4 years post frostbite We listed some eighteen possible complaints on the frostbite questionnaire but I have listed here only the six most common complaints These symptoms are listed in the column to the left and represent complaints during summer months and winter months of patients with various degrees of cold injury The significant thing is that symptoms in all cases except one are much more marked during the cold or winter months than during the summer months the one exception being excessive sweating

Schatzki What usually were the joint symptoms? Were they pain?

Blair The joint symptoms may be either stiff joints or joint pain and we asked on the questionnaire the two questions Joint stiffness? Joint pain? The number given in Table VI is the total of both joint pain and joint stiffness Of the two I believe joint pain complaints were a little more numerous

Schatzki Do you think that this might be very markedly colored by compensation questions because as far as I remember when we saw the soldiers about 15 months after the cold injury not a single one of them complained about joint pain

Blair Joint pain appears to have increased but I wonder if much of it is not on a psychogenic rather than organic basis and it may very well be tied into this disability compensation factor because most of these men understandably are always quite concerned over the possibility of losing any compensation they may be getting Others who do not have disability compensation are constantly writing for information that they might use in trying to obtain a disability rating

Talbott How many of the 50 examinations did you conduct yourself all of the 50?

Blair All of the 50

TABLE VI

Symptoms of Patients 4 Years After Cold Injury

Symptoms	2d Degree Frostbite		3d Degree Frostbite		4th Degree Frostbite	
	Summer	*Winter*	*Summer*	*Winter*	*Summer*	*Winter*
Cold feet	0 (0%)	8 (80%)	19 (28%)	55 (83%)	3 (20%)	10 (67%)
Pain	3 (30%)	7 (70%)	29 (43%)	46 (69%)	10 (67%)	12 (80%)
Excessive sweating	8 (80%)	8 (80%)	54 (81%)	33 (49%)	11 (74%)	8 (54%)
Numbness	2 (20%)	7 (70%)	20 (30%)	49 (74%)	7 (47%)	10 (67%)
Abnormal color	2 (20%)	4 (40%)	22 (33%)	43 (65%)	7 (47%)	7 (47%)
Joint symptoms	1 (10%)	4 (40%)	17 (26%)	26 (39%)	5 (33%)	7 (47%)

Talbott What were you impressed with 4 years later looking at the feet?

Blair Table VII shows the physical findings 4 years post frostbite on those cases that Dr Talbott asked about Again, I have listed the six most significant or most common findings in these individuals Tissue loss, of course, does not occur in second degree cases, by definition In third degree cases the tissue loss is what we call a tissue defect It is not loss of a part but rather "punched out" areas that will be shown in later photographs A tissue deficit results from sloughing of the eschar and subsequent granulation of the lesion Of course, tissue loss occurs in all fourth degree cold injuries

Scars are absent in "ill defined condition of the feet" and can rarely be seen in second degree lesions At least, they were not seen in any second degree injuries that I observed They are usually present in third degree, and of course always present in fourth degree

Abnormal nails are probably the most unexpected finding that I observed in looking at these men If the degree of the cold injury is severe enough to be of full skin thickness in more than two thirds of the cases there are definitely abnormal nails present The nails are markedly thickened heavily ridged, and contracted down at the front margin In fourth degree where we listed four cases as representing 100 per cent, it is because five patients had

TABLE VII

Physical Findings in Patients 4 Years After Cold Injury

Physical Findings	Frostbite 2d Degree	3d Degree	4th Degree	Ill defined Condition of Feet
Tissue loss	0 (0%)	23 (66%)	9 (100%)	0 (0%)
Scars	0 (0%)	32 (91%)	9 (100%)	0 (0%)
Abnormal nails	0 (0%)	25 (71%)	4 (100%)	0 (0%)
Hyperhidrosis	3 (75%)	12 (34%)	5 (56%)	1 (50%)
Abnormal color	2 (50%)	14 (40%)	7 (78%)	1 (50%)
Stiff joints	1 (25%)	7 (20%)	6 (86%)	0 (0%)

no nails to be examined and all four that had nails still present showed a pathologic condition

The hyperhidrosis or excessive sweating was observed in a rough manner in which upon beginning examination of these men s feet the feet were dried with a towel before any studies were made and then after visual observations were completed and a period of 10 minutes had elapsed, the feet were examined for the degree of sweating present

In the normal individual the foot will feel slightly moist and warm after 10 minutes exposure to room temperature In individuals who have had sympathectomies the foot is usually quite dry and very warm In most of these cold injury cases, the foot was actually dripping perspiration 10 minutes after having been dried It was purely a qualitative evaluation of sweating by observation and palpation

This brings up a point, is it a cause or is it an effect? We cannot answer that The person who is hyperhidrotic is a very likely candidate for cold injury and the hyperhidrosis may have been present before cold injury and may have been a major factor in causing the injury

Sweet Would you try to evaluate that by determining whether or not there was any such response in the hands of the individuals? Presumably hyperhidrosis in the hands might have been a pre-injury phenomenon

Blair That is a very interesting suggestion Dr Sweet I only wish you had suggested it to me before I had seen the fifty men

a vasospastic syndrome that remains persistent over many years Among those who have also had ulceration of the skin, a patient in whom the hyperhidrosis is sharply limited to the area around the ulcer will occasionally be found The foot in such a patient will be dry, but the region around the ulcer itself will be bathed in sweat On the other hand, there are other patients with similar ulcers in whom the hyperhidrosis involves the entire foot as well as the skin about the ulcerated area

Horvath There is no question but that there is a marked difference in the sweating produced in different parts of the foot and I think the question Dr Burton asked is really apropos Is this greater near the area of the injury compared with what it would have been before?

Shumacker I would certainly agree

Burton I would like to make one point while we are on hyperhidrosis, and discussing the "psychic" causes These are not confined to anxiety In our field survey on boots we found by questioning 500 men and repeatedly asking them over a period of 6 weeks whether their feet sweated a lot, a little, or not at all that the correlation of the reports of sweatiness of their feet had nothing to do with the thermal environment, or whether they were cold or warm It was however, very strongly correlated with any reports of discomfort In other words if an individual is uncomfortable for any reason his feet sweat and I think we all have experienced this If a shoe hurts a bit both feet begin to sweat The phenomenon isn't "psychic" in the sense that it must be caused by "anxiety" since any discomfort factor will cause sweating I can well believe that these people who have some excessive sweating will sweat a lot more when they are uncomfortable

Fremont Smith Pain will do it It is a sympathetic reaction isn't it?

Has the reactivity of the vessels in these injured feet been tested? What would happen to blood flow in one foot if the other foot was put in cold water?

Blair Yes, to a limited degree we did carry out some vascular observations We used some of the methods that Dr George Burch employed on trench foot patients during World War II and on which he reported in the Johns Hopkins Hospital Bulletin (8) We did a series of very simple and rather crude studies, what is called a "refilling time of skin vessels" test, devised by Dr Burch The large toe is held between three fingers, firmly pressed for a

period of several seconds, usually 3 seconds, emptied of all its blood by pressure, and then suddenly released The time in seconds required for the blanched area to regain its color fully is measured with a stopwatch Our data indicate that there was some kind of pathologic condition of the circulatory system

Fremont-Smith Slowness of return?

Blair No, cold injured toes refill more rapidly It is explained primarily by loss of tone in the vessels of the injured toe, and all of Dr Burch's studies on trench foot patients showed a more rapid refilling time than normals, particularly after a period in a cool room

Fremont Smith Is that presumably a venous refilling, not from the arterial side?

Blair It is probably a combination of both, but it is described as an injury producing loss of tone in the vessels so that they are in shall we say a state of nonresistance to blood flow Thus, they refill more rapidly following emptying by pressure

Fremont Smith What is the position of the toe? Is it below heart level? If it is above heart level you would be sure it is not venous

Blair It is roughly at heart level The man is lying flat on an Army cot or hospital bed Visual observations are carried out while the patient stabilizes in a horizontal position The large toe is firmly pressed between the two fingers and thumb for a period of 3 seconds then suddenly released, and the return to color timed with a stopwatch The usual figure for a normal subject in a cool room is quoted as being between 10 and 12 seconds for full return of color We found in our frostbite cases that the minimum was 6 6 seconds and the maximum refilling time was 10 6 seconds The average was 8 3 seconds and that is in about the same category that Dr Burch recorded for his trench foot cases He stated that the part is not normal if the refilling time is less than 8 0 seconds

A much better way of studying the reactivity of the vessels, Dr Fremont Smith is the one you suggested, i e by immersing one foot in cold water and seeing whether or not there is an observable vasoconstriction in the other

We started out to do just that on these cold injury cases with a portable skin temperature apparatus but ran into almost impossible conditions One must have a constant temperature room no interruptions, and no psychogenic disturbances of the patient from apprehension, noise or people These conditions were so poorly

controlled and our results so unsatisfactory that after carrying out this test on a smaller number of patients we dropped it as being impossible to do accurately or to get interpretable data

Fremont Smith If the leg is slightly raised so that the toe is very distinctly above heart level, you would be able to differentiate whether the fill is venous or not

Burton Dr Fremont Smith I think we now know, from the work that Dr P Gaskell (4) has been doing, that the toe cannot fill except from the arterial side The valves apparently are very effective and one cannot get filling except from the arterioles

Fremont Smith Even in a pathologic situation?

Burton I would not know about that

Fremont-Smith That is interesting and probably proves that *this is an arterial refilling and there is a vasodilatation or failure* of vasoconstriction

Horvath Therefore, a very good test must be Dr Burton's critical closing pressure that he has been working on for a number of years If it is arterial reactivity, this critical closing pressure should change

Fremont Smith What is critical closing pressure?

Burton If small blood vessels are under tone, the muscle in their wall is tending to make them smaller The physics of this indicates (and this works out experimentally) that if the pressure within them falls below a critical value they will close completely If the pressure within the lumen (or the translumen pressure is a better word) at which they close is measured, then this is a good measure of the tone

Kark Among these 50 men were there no examples of Raynaud's phenomenon?

Blair We will talk a little about this right now if you like, for we are now down to abnormal color in our physical findings which is a good place to bring it in *This matter of abnormal color is a* rather difficult thing to evaluate particularly in the white patient, because there are so many factors of dependency, psychogenic effects, and vasomotor responses In the Negro soldier it is primarily a depigmentation phenomenon rather than one of abnormal color If the cold injury is as severe as third or fourth degree, then almost without exception there is marked depigmentation present in the Negro

So far as Dr Kark's question about Raynaud's phenomenon is concerned, a constant temperature room is needed to evaluate it properly, and again we ran into the same difficulty of having all types of psychogenic disturbances and anxiety responses of the patients Under these conditions I was unable to make any decision as to presence of Raynaud's phenomenon in these patients

I do not know whether Dr Shumacker, from his experience in looking at these types of cases, would have any comment

Shumacker I can only say this, Colonel Blair I have seen a few patients who, following what I felt was true frostbite or trench foot, have developed a clinical picture that was hardly distinguishable from true idiopathic Raynaud's disease

Kark Of the hands or the feet?

Shumacker Of both, I think, but I am not absolutely sure The cases that come to my mind at the moment had involvement only of the hands

Sellers Were the hands injured, or the feet?

Shumacker The hands

Montgomery It showed up quite a little later, didn't it?

Shumacker Not necessarily For example, Dr Montgomery during World War II, I saw a female patient who had sustained severe frostbite of both hands She had always had beforehand, as far as one could tell from her history, perfectly normal vascular tonus She had been on guard duty one very cold below-freezing night and by the end of her tour of duty had cold stiff hands which subsequently developed edema, erythema and, as I recall, vesicles Within a period of months, or certainly by the next winter, she had a severe Raynaud's disorder For the first time in her life whenever she was exposed to cold she developed the characteristic color changes coldness and numbness of her fingers When she would return to a warm environment her fingers would regain normal circulation At the time I saw her it was easy to reproduce this phenomenon of digital spasm Amazingly enough, she developed scleroderma rather rapidly after the onset of this Raynaud's syndrome

Montgomery That would make it suspicious that the underlying disease was there before the exposure to cold

Shumacker Except that the history was absolutely negative up to the moment of the frostbite and the onset of her vasospastic difficulty was only a short while afterward I have seen quite a

controlled and our results so unsatisfactory that after carrying out this test on a smaller number of patients we dropped it as being impossible to do accurately or to get interpretable data

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The question arises what physical find bitten patients 4 years after injury? Wh be seen when these patients are exam

In first and second degree cold injury th ing is so complete that on physical examin tically nothing suggestive of a previous fr was third degree meaning full skin thick ings became quite evident and relatively group If the injury is so severe as to be obvious that the findings are quite distin

The Negro patient whose feet are shown degree injury of his left foot and a fairly volvement of his right foot Of course in th loss the scarring and the deformity caused toes overlying the tissue defect are quite obv foot which had a third degree injury there is there is marked depigmentation over the injured a nails are greatly thickened heavily ridged pathologic ap ance, and the nail beds have a dark or abnormal appearance



FIGURE 1 Feet of negro patient 4 years after fourth degree frostbite (depigmentation and deformity of left foot shown)

number of individuals who developed the same picture of a Raynaud like disorder after frostbite or trench foot She is the only patient I recall who developed scleroderma as well

Talbott It was localized scleroderma?

Shumacker It was localized to the hands yes

Talbott It wasn t on the face and other parts of the body?

Shumacker No it was severe in the fingers and minimal over the dorsal surface of the hands

Montgomery White and Scoville (5) published some work on cases of excessive vasomotor tone long after the exposure to cold

Shumacker That is right I am sure Dr Simeone must have some information about this matter

Simeone Our data on the follow up of World War II veterans are not yet completed but in the sample studied some 4 6 per cent of the group had Raynaud s phenomenon until the time they were discharged from military service I do not know the figures for the later follow up

Montgomery Was that with or without Raynaud s phenomenon in the hands?

Simeone Without involvement of the hands

Montgomery That is critical because Raynaud s phenomenon is much more common in the hands than in the feet

Blair In making my last point namely the stiff joints I would like to mention two or three things One is that the actual finding of stiff joints is well below the frequency of joint stiffness complained of by the patients (Table VII) One other thing that is important is that the presence of these stiff joints does not necessarily imply any pathology within the joint itself because all fourth degree cases are very heavily scarred with a large amount of scar tissue overlying the joints which in itself may restrict joint movement We did not report a positive finding of stiff joints unless we could demonstrate at least 50 per cent loss in mobility of the joint But this does not always indicate true joint changes

There is another factor that should be mentioned as relating to all the physical findings in Table VII The fourth degree findings as well as symptoms are qualified by the fact that of the nine fourth degree patients three had had lumbar sympathectomies for relief of existing symptoms prior to our examination

Thus there are at least four, and possibly five criteria to look for in a mildly cold injured person as definite evidence of previous cold injury One is the condition of the nails second the presence of any area of scar tissue third a tissue deficit fourth a pathologic condition of the joints and fifth color changes particularly depigmentation in the Negro patient

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In a patient who is as severely injured as this, it becomes obvious that he has had quite severe cold injury, but the more difficult ones are those with very mild third degree frostbite where it is necessary to know what to look for in order to confirm definitely a history of previous cold injury The patient whose feet are shown in Figure 2 had a mild third degree frostbite of the left foot and no injury at all of the right foot The injury consisted of a dime sized bleb or blister and full skin thickness on the medial aspect of the large toe If the left large toe is compared with the right large toe, a little area of scar tissue about the size of a dime can be seen at the tip of the toe

But more striking are the two large toenails themselves The nail of the left large toe is greatly thickened as compared with the right one The nail is constricted quite markedly at the front and is heavily ridged as compared with the right one The left nail bed gives a totally different appearance from the right nail bed, being abnormally dark in color

The soles of the feet in Figure 2 show that the large toe of the left foot has a rather marked tissue defect on its medial tip as compared with the right large toe



FIGURE 2 Feet of white patient 4 years after third degree frostbite (thickened nail and tissue defect of left big toe shown)

ROENTGENOLOGIC CHANGES IN BONES FOLLOWING COLD INJURY IN MAN*

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WHEN I WENT TO FORT KNOX to look at these cases described by Colonel Blair, I knew nothing about the roentgen ray changes in frostbite and I purposely did not read up on the subject before I went there because I wanted to be as unbiased as possible

Colonel Vinson and I went through the films of extremities that had been collected on 100 soldiers, case by case, just trying to see if there was anything in these feet which was different from the feet I usually see regardless of how badly or how little they had been frostbitten

Certain patterns of bones changes became apparent and these we grouped Then we went through all the cases again, trying to evaluate them with these groups in mind

Group I was composed of cases who showed no abnormal radiologic changes whatsoever, and among this group were some of the most severely frostbitten soldiers No osteoporosis or bone destruction can occur in toes which are completely cut off from circulation For that reason the phalanges of gangrenous toes appeared normal whereas the less injured metatarsals of the same foot might easily show osteoporosis

As far as osteoporosis is concerned it is a well known fact that it is very difficult to evaluate the degree of calcification or decalcification of bone even under the best circumstances The films we were examining had been taken in various military installations first in an evacuation hospital, then in Japan and then in the Zone of the Interior So it was very difficult to compare the different

*The work here reported was supported by Contract No DA49 007 MD 342 between Harvard University and the Office of the Surgeon General Department of the Army

The medical histories clinical summaries physiologic data serial photographs and serial roentgenograms used in this study have been indexed and filed in the library of the Army Medical Research Laboratory Fort Knox Kentucky and are available to any interested students or investigators



FIGURE 4. Development of juxta-articular subchondral defect. (A) 2 months, (B) 7 months, (C) 12 months and (D) 4 years respectively following frostbite. Defect first visible 7 months after frostbite [heads of fifth proximal and fourth middle phalanges (B)]

by some nerve or vascular mechanism but simply follow exposure of bone to the outside world

The bone changes which particularly interested us were those seen in later months near joints Figure 4(*A*) shows, for instance, the fifth and fourth toes of a soldier 2 months after the frostbite and they look perfectly normal Figure 4(*B*) shows them 7 months after the frostbite There is a little deformity of the proximal interphalangeal joint of the fifth toe and a little deformity of the distal interphalangeal joint of the fourth toe A year after the frostbite, 5 months later there were very definitely changes of these two joint surfaces apparently produced by subchondral bone defects [Figure 4(*C*)] There are a few reports in the literature about isolated cases of similar joint changes dating back to 1930 (1-4)

As to what happens to these joint changes during the later follow-up this same patient 4 years later [Figure 4(*D*)] showed that the joint defects were still there, but they were surrounded by dense bone In some of these cases the joint lesions had definitely regressed at the end of 4 years while in others new lesions had occurred

Hedblom Was there any change in the subjective symptoms in the patients? Were their feet more or less comfortable?

Schatzki I saw several of these soldiers with joint injuries at Fort Knox about a year to fifteen months following the frostbite and at that time we could not elicit any complaint in regard to the joints in any of them The involved joint of one of the soldiers was a little stiff This picture changed in later follow up As Colonel Blair said earlier there was quite a number of soldiers who later complained about joint pain As a matter of fact the majority of the soldiers with roentgenologic joint changes had joint pain by that time but so had others who did not have any roentgen ray changes One obviously wonders how many of those complaints are really caused by what one sees roentgenologically

Hedblom But none of those with radiographic joint changes were free of pain?

Schatzki I do not know about that Is that correct?

Blair *We would have to go through all the histories to check,* Dr Schatzki but definitely not in the case that you have just shown

Schatzki Yes

Blair This patient said that he never had joint pain during summer or winter In the winter he complains of some stiff joints, but he does not complain of pain at any time

Talbott What was the degree of involvement originally on that foot?

Blair His was a third degree frostbite case involving both feet

Talbott But the fifth toe is the one that is the most affected

Blair All toes were swollen in appearance and they had superficial vesicles on the dorsal portion of both the great and the second toes The joint changes here are in the first and second toes, aren't they?

Schatzki And the fourth and fifth

Blair That does not rule out the fact that he may have had involvement there, too

Schatzki For some of the soldiers there was such a very detailed description of the foot that we could establish almost digit by digit what degree of frostbite was present In most instances they had third degree frostbite A few of them had second degree and I think at least one of them had only first degree frostbite of the involved toe

Blair He did have involvement of the fourth and fifth toes I would say that he probably had a second degree involvement of the fourth and fifth toes

Shumacker On looking at the colored transparency one would say that the fifth toe was the last one to heal and that it was the site of third degree damage

Blair Yes, he had third degree damage of the fourth and fifth toes

Shumacker Do these cystic changes, in your opinion resemble in any way those seen in gout?

Schatzki Not so much the ones in gout but I would say they are similar to what is seen in degenerative arthritis and occasionally in rheumatoid arthritis The gout lesions vary markedly in size They are usually much larger The late joint changes seen following frostbite are much more homogeneous in character and size than are gout lesions

Horvath What about following severe burns of the feet?

Schatzki I have no idea

Horvath I would like to raise a question is this a specific or a nspecific response to damage which has been going on prior exposure?

Montgomery That might be difficult to establish

Schatzki Hands apparently are much more apt to undergo nt changes In our material the total number of frostbitten hands s rather small but of the 11 soldiers who had frostbite of the nd 4 showed late joint changes whereas of the approximately who had frostbitten feet only 11 showed late joint changes

This difference may be significant The question of whether all ldiers were really frostbitten or whether some only had trench ot injuries was discussed earlier this morning We do know that l injured hands were really frostbitten The presence of such nt changes perhaps proves the real frostbite nature of the injury at least do not know of similar lesions combined with trench immersion foot

Horvath I wondered because it certainly looks like a nonspecific action

Schatzki Yes This question I am sure will come up after we ve seen some of Dr Kulka s specimens

Shumacker One thing that comes to my mind and I do not now whether it has any real pertinence at all is that in a very nall percentage of patients with Raynaud s disease or a Raynaud ke disorder there is an associated arthritis I suppose many of u have observed this association on occasions I recall one oman who had a very disabling Raynaud s disorder affecting all ur extremities and very severe scleroderma of the hands She ad rather diffuse arthritic complaints and she had cystic changes hich were somewhat like these under discussion They were iggestive enough of gout to warrant studying her from this stand oint We were not able to establish gout as the diagnosis how ver She is the only patient I have seen with Raynaud s disorder nd arthritic complaints who had cystic bone changes They were ot too dissimilar from these under discussion

Talbott Dr Schatzki I would feel that the roentgenologic hanges that you have described are more closely related to those f rheumatoid arthritis or degenerative disease Certainly the cystic hanges that Dr Shumacker has described do not mean gout at all

Shumacker No

Talbott The cystic changes are the items that may be confused

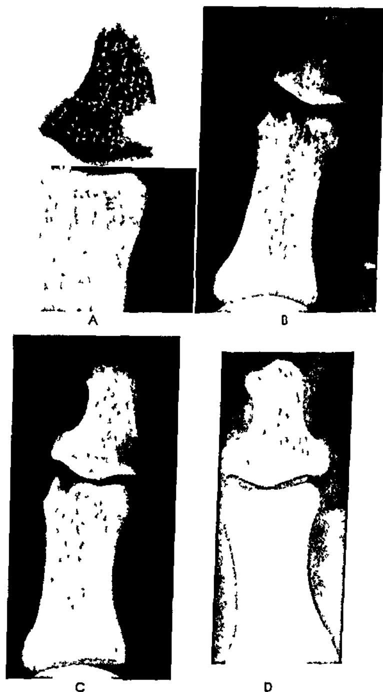


FIGURE 5 Development and 4 year follow up of subchondral juxta articular defect of interphalangeal joint of great toe (*A*) 3 months (*B*) 8 months (*C*) 1 year, and (*D*) 4 years following the frostbite Clinically third degree frostbite

Shumacker That is correct

Talbott I think the distinct changes were narrowing of the joint space These are the changes we see characteristically in rheuma toid arthritis and sometimes in gouty arthritis

Schatzki The thing that makes them different from rheumatoid arthritis is that one does not see any late osteoporosis with it nor any joint fusion We have not seen a single joint which fused

Talbott Then we can simply say that these may be similar to rheumatoid arthritis in an earlier stage because joint fusion is a late stage of the disease

Schatzki Obviously they are subcartilaginous defects and the same happens in rheumatoid arthritis

Conn Could this be compatible with a form of traumatic de generative arthritis?

Schatzki Yes I think it could be I have asked myself quite frequently Is there any possibility that these patients have just used their limbs in a different way and therefore these changes have occurred? I think that is what you were leading up to

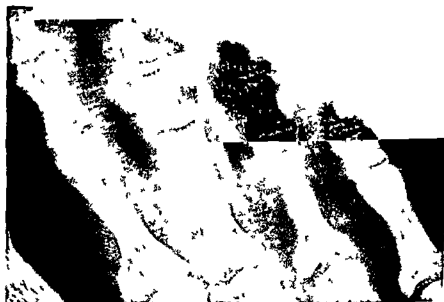
Conn Yes I was wondering whether under the conditions of acquisition of this lesion it might not be that trauma played an important early part the degenerative lesion develops at a later date but the traumatic incident occurs early

Schatzki This is difficult to say but I think there is a definite possibility that some mechanical static factor may play some role In favor of it is the distribution of the lesions The vast majority of the lesions occurred in the fifth toe and not in the great toe which is the most commonly involved toe clinically What is the relative frequency of clinical frostbite of the first to fifth toes Colonel Blair?

Blair In the 100 cases I cannot give you the exact number but the first toe is by far the most frequently involved and then usually the second and fifth toes

Schatzki In Colonel Orr's paper he says that clinically on the right side the first toe was involved 36 times and the fifth toe 22 times and on the left side 38 to 6 The higher incidence of joint changes in the fifth toes must have some significance and I would not be surprised if static factors enter in there

Figure 5(*A*) shows a man 3 months after the frostbite The toes are perfectly normal Figure 5(*B*) shows the early defect in the interphalangeal joint of the great toe 8 months after the frostbite



A



B

FIGURE 6 Development and 4 year follow up of juxta articular bone defects in 25 year old soldier with second degree frostbite (*A*) 3 months no pathology except for some osteoporosis (*B*) 7 [illegible]
joints of second and third toes (S [illegible]
Vinson H A and Schatzki R [illegible]
frostbite Korea 1950 51 *Radiology* [illegible]

Figure 5(*C*) shows that a year after the frostbite there is a very definitely established defect here Figure 5(*D*) is 4 years after the frostbite and healing is evident in one of the defects Offhand I do not remember that I have seen such nice healing in patients who had degenerative changes This patient by the way, had similar changes in the little toe of the same foot Does he have any disability?

Blair He complained of some joint pain primarily in the right foot as compared to the left and he complained of stiff joints in the right foot but not in the left

Hedblom How long was that other man off his feet?

Blair He was off his feet roughly for the major part of his first 6 weeks in the hospital but he was hospitalized for 6 months That was his total period of hospitalization from the 15th of January until the 15th of June of 1951 6 months of hospitalization with approximately 6 weeks off his feet

Schatzki Figure 6(*A*) is the 3 month film of the next patient It shows nothing abnormal except for some decalcification which later disappeared Figure 6(*B*) shows that 7 months after the frostbite some very tiny joint defects become visible which are marked at the end of 14 months [Figure 7(*A*)] Then round defects which do not seem to be connected with the joint can be seen I rather think that they probably are and that they are on the edge of the joint in front or in back in other words a face on view of the lesions It is however possible that they are actually separated from the joint by some normal bone We have no way of knowing On the anteroposterior and oblique views which we had at our disposal they never were definitely proved to be connected with the joint

Figure 7(*B*) is the same foot 4 years later There is some filling in of some of the defects The patient showed very similar lesions in both feet In contrast to one foot the lesions of the other foot are almost unchanged 4 years after frostbite (not illustrated)

Horvath Were both feet involved?

Schatzki Yes both feet were involved The films of the hands shown in Figure 8 belong to another soldier He had taken his gloves off in order to warm his hands at a fire Then the enemy started to open fire He jumped into a foxhole and his hands were exposed to the cold for several hours He developed a third degree frostbite



A



B

FIGURE 7 Same soldier as shown in Figure 6 (*A*) 14 months after frostbite obvious defects of the middle phalanges of the second third and fifth toes (*B*) 4 years after frostbite partial healing of defects Reprinted by permission from Vinson H A and Schatzki R Roentgenologic bone changes encountered in frostbite Korea 1950-51 *Radiology* 63, 685 (1954)



FIGURE 8 Development of subchondral defects in a finger (A) 1½ months (B) 9 months and (C) 18 months after frostbite



A



B

FIGURE 9 Four year follow up of joint changes (*A*) no joint changes 6 weeks following frostbite and (*B*) 4 years following frostbite (the terminal phalanx of the middle finger has been amputated) There are subchondral defects seen in the distal interphalangeal joints of the second and fourth fingers Clinically third degree frostbite

The joints appear normal 3 months after frostbite Slight defects of the joint surfaces are visible at 8 months after frostbite [Figure 8(*B*)] They are very marked 16 months post frostbite [Figure 8(*C*)] He also had changes in three other fingers two on the same hand and one on the other hand Unfortunately we have no late follow up films of the lesions

Figure 9(*A*) shows another soldier with a similar story He lost his glove This is the 6 week film following the injury and it shows normal joints then there are no films until 4 years later [Figure 9(*B*)] One phalanx had been amputated The joints in the two adjacent fingers show sharply defined defects of their surfaces When these films are examined closely it will be observed that the trabeculation of these fingers down to the proximal inter phalangeal joints has changed compared to the original film The trabeculae are a little more widely spaced and thicker not quite as in Paget s disease but there is a change in that direction The changes are so small that I only became interested in them after I saw the lantern slides of the individual phalanges Once I realized them however I recognized them in a fairly high percentage of those soldiers who had joint injuries

Talbott Would you define joint injury?

Schatzki I was talking about the roentgenologic changes close to joints

Talbott The cystic changes?

Schatzki Juxta articular changes

Montgomery Is the appearance of this very different from that of diabetic neuropathy as opposed to that of the ischemic tissue of the diabetic?

Schatzki They are different although very early diabetic arthrop athy may look somewhat similar

Montgomery I was wondering if there might be a common factor such as damaged nerve playing a part in both diseases

Schatzki I do not think so I believe the diabetic changes are similar to those seen in tabes They represent abused joints in patients who have lost sensation and do not protect the joints normally The frostbitten patients as far as I know or could learn from Colonel Blair do not have these neurological defects so this is on a completely different background

Talbott They may have the same subjective symptoms that a diabetic patient has at times in which it is not possible to demon strate much Isn t that right Dr Conn?

Conn Yes However, by the time changes in roentgenograms of the joints can be seen, the typical Charcot joint results, in which there is very little sensation But I have been thinking along those same lines, because in early diabetic neuropathy, before anything but sensory changes can be demonstrated, at least before fibrotic or sensory changes have been seen, hyperhidrosis has not been an uncommon finding

Montgomery Those I have seen in diabetic neuropathy were hypohidrotic

Conn They were hypohidrotic later, but in the early stage they were hyperhidrotic

Question In the diabetic neuropathy, isn't there severe pain as a very common sensation?

Conn A burning sensation

Montgomery And often not severe

Conn Not often severe

Schatzki I cannot quite conceive of these changes being on a Charcot joint basis First, I think at no time were any neurological defects demonstrated, and then secondly, the joint lesions some times healed later

Shumacker They did not have any demonstrated sensory deficit did they?

Blair Not that we could detect We had a laboratory set up at the Army Medical Research Laboratory at Fort Knox whose primary function was a sensory study on these individuals, consisting of tactile sensation, temperature pain and proprioception studies and the findings were all essentially negative in these cases

Conn But during these 7 hours of exposure, while they were getting this lesion, they had no sensation

Blair Essentially one of cold first then superseded by numbness That was characteristic

Conn And injury at that time could have come quite easily inasmuch as there was very little protection by way of sensation

Montgomery Especially if the tissues were hard all the way through

Conn Yes

Schatzki Do you think there can really be that much damage from abusing limbs in that short period of time?

Conn I wonder whether an animal with feet completely anesthetized for 4 hours wouldn't injure his joints quite severely while walking around

Kulka How about cases of sprained ankles which were injected with novocain? Might they serve as a control group?

Conn I do not think that tactile sensation is abolished by that procedure, is it?

Simeone No

Schatzki For instance, in the man who lost his glove and was severely frostbitten, do you think he made much use of his hands during those hours while he was exposed?

Conn I do not think he made any use of them but he may have bounced them around and not known what he was hitting

Montgomery You mean he might have torn tissue in the period of solidification or during the beginning of thawing beyond what he might otherwise have done?

Conn Otherwise, yes

Schatzki Your theory is difficult to disprove Figure 10 is the finger of another frostbitten soldier with late joint defects and late trabecular changes The bone looks "older" on the last film than it does on the earlier film I do not know if that has anything to do with the injury *per se* Dr Kulka would like me to assume that, from his rabbit findings I wonder, however, if these changes are not simply a result of changed statics They look so much like what we see otherwise following changes in statics for instance, the pattern of the femur after injury to the spine, that I am rather inclined to think at the present time that these changes are not caused by the frostbite injury but by adaptation of the trabeculae to changed static conditions

Horvath There are two changed conditions here One is age and the other is probably disuse

Schatzki Age plays no role I think

Horvath But 4 years is 4 years

Schatzki Not in this age group This is the only time when in our lives we have "normal bones i e between 20 and 30 and the patients were practically all in that age group

Horvath Even between 20 and 30 some changes must be occurring

Schatzki Not discernible ones

The man is going to walk just about as much as he ever did and if we leave on his great toe we do not interfere with his gait Isn t that right? You do not interfere nearly as much if you take off a fifth or a fourth toe but if you take off his great toe he will have a hitch in his get up

Fremont Smith Isn t the issue here whether or not a minimum or a slight change in use or disuse such as you speak of Dr Horvath in this situation could cause this degree of atrophy? I was under the impression that there really had to be a considerable degree of disuse to show atrophy of disuse by roentgenogram but is that true?

Horvath These are relatively minor changes in the first place aren t they?

Montgomery The degree of disuse is very considerable

Schatzki These trabecular changes were so small that I missed them when I went over the films the first time

Horvath The first point is that they are minor changes and therefore they are minor degrees of disuse that might cause this Ordinarily we think of rather large degrees of disuse and corresponding huge changes in the bone

Fremont Smith How long must a limb be immobilized completely for any roentgenologic changes to be found as a result of disuse?

Schatzki I cannot answer that exactly but very little time is needed I think it can happen within 4 weeks certainly

Talbott If the limb is in a cast it certainly can

Schatzki Even in less than 4 weeks

Fremont Smith This brings out the point very clearly and I think you are right

Montgomery You mean loss of bone in the joint?

Schatzki I have never seen joint changes produced by disuse

Horvath This was in the bone itself Is it not in the joint?

Shumacker Perhaps we should start over by stating what one sees with disuse only One sees just demineralization doesn t he Dr Schatzki?

Schatzki That is right probably a little more than that However we are talking about two different things here First there are the very definite discrete changes which we call the juxta articular changes those little defects of the joint surfaces then

there are the minor changes in the whole bone As far as the juxta articular changes are concerned they will not occur just from disuse as far as I know

Horvath That is right

Schatzki The minor diffuse bone changes look different from what one sees in acute disuse and they look different from what one sees even in long standing disuse They look a little like what one sees in changed use

Horvath Yes You think the juxta articular changes are not related to the aging of these individuals?

Schatzki I do not believe that they have anything to do with the aging of these individuals Normally people in this age group have the nicest looking bones one can see anywhere They do not get these changes unless they have suffered an injury to the bone then of course they do

Horvath They may have had an injury indirectly to the bone and therefore this is showing up speeding up the injury

Schatzki What kind of injury?

Horvath Nutritional

Schatzki Dr L Henry Garland of Stanford University San Francisco when discussing Colonel Vinsons and my paper (5) wondered whether these could be degenerative changes which these soldiers might have gotten anyway even without frostbite In my opinion young people do not develop such degenerative joint changes without obvious "injuries

Horvath Of course the joints that I have seen have been the knee joints primarily and there a quite marked aging change which is variable among different individuals can be seen

Blair In the 20 year group?

Horvath You do not see many 20 year olds with much change but there are some You cannot tell whether it is a beginning aging process or aging *per se* until you follow them along but I thought it might be conceivable that there may be a factor here This is a weight bearing area just as much as the knee is

Schatzki The joint changes in these frostbitten soldiers occurred also in the fingers where there was no factor of weight bearing As a matter of fact some of the most striking changes were in the hands I am convinced that aging has nothing to do with these lesions

Figure 11 is not of a soldier It shows the radiograph of the first case with joint changes described in the literature Lohr (1)



in 1930 described this single case a boy who while bicycling froze his hands He shows changes in those two joints and they are very similar to what we saw in our cases This was a 16 year old boy and this film was taken 9 months after the frostbite

Kulka Was there real icing of the tissues in Lohr s case?

Schatzki This boy wore gloves and in spite of that he had developed severe blisters when he went to the University Hospital one day after the injury

Sellers Was that an intra articular change? It looked like it in the film

Schatzki Yes I think most of the changes we saw were intra articular I used the word juxta because in a few of them we could not really prove that they were intra articular

I would like to present a few statistical facts in regard to the joint changes The fifth toes were involved in twelve instances considerably more frequently than the other toes (the first and fourth toes five times each and the second and third toes three times each)

The proximal interphalangeal joints showed changes more frequently than the distal interphalangeal joints (16 involved proximal interphalangeal joints to 9 involved distal interphalangeal joints) The metatarsophalangeal joints were involved in only two instances In the hands which showed joint changes the fifth fingers and the proximal interphalangeal joints were likewise most commonly affected It is of some interest to see how soon after the frostbite the joint changes became noticeable In none of the fifteen cases with joint changes were they visible before 5 months post frostbite In ten cases they were seen within the first year post frostbite In the remaining five cases they first showed up on the radiographs taken at the time of the 4 year follow up Some of these soldiers however had had no opportunity to demonstrate earlier joint changes since their last radiographs prior to the 4 year follow up had been taken within the first 2 or 3 months following the injury In other words of eleven cases with adequate follow up ten showed joint changes first within the 5- to 12 month period following the frost bite and only in one case did changes appear later

I would like to say a few words about some other radiological changes which are of interest in regard to those seen in the rabbit experiments Among the 100 soldiers there were only two with periosteal new bone formation around the injured digits in contrast to the frostbite rabbits which showed such new bone forma

tion very commonly. This is the little toe of one of the two a month and a half after the injury [Figure 12(*A*)]. A small amount of the new bone formation can be seen around the proximal *phalanx and also the corresponding metatarsal bone. In addition* there is a small area suggestive of destruction in the phalanx. There was a blister over this toe. The record at no time indicates



FIGURE 12. Transient periosteal new bone formation (*A*) 2 months, (*B*) 4 months and (*C*) 4 years after frostbite. Reprinted by permission from Vinson, H. A., and Schatzki, R.: Roentgenologic bone changes encountered in frostbite, Korea *1950-51*. *Radiology* 63: 685 (1954).

that the patient had clinical osteomyelitis but at the end of 4 months this defect had almost healed [Figure 12(*B*)] The new bone formation was decreasing and at the end of 4 years the toe appeared normal [Figure 12(C)]

The other case was a 17 year old boy who 5 weeks after the injury showed some very early periosteal new bone formation about the fifth metatarsal bone and a little more at 9 weeks (Figure 13) The 13 week film shows that it is almost gone

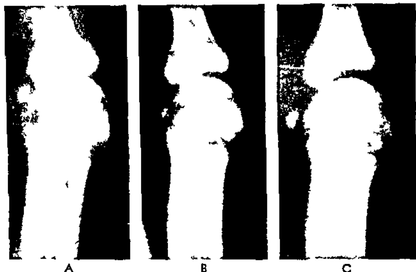


Figure 13 Transient periosteal new bone formation about the head of the fifth metatarsal of a 17 year-old soldier close to growing epiphysis (*A*) 5 weeks (*B*) 9 weeks and (*C*) 13 weeks after frostbite (See also Figures 14 and 15)

The new bone formation was close to the open epiphyseal plate and the injury resulted in a growth disturbance of the epiphysis (Figures 14 and 15) In addition the radiographs 4 years after the frostbite show diffuse changes in trabeculation of the involved toe and metatarsal bone as seen in the late follow ups of some of the patients with joint changes

The next case (Figure 16) which is not a soldier but a child which was seen recently at the Massachusetts General Hospital will illustrate more dramatically the growth disturbance which may be caused by frostbite as found by Dreyfuss and Glimcher (6)

Kark Did you obtain any specimens from these bones for biopsy?



FIGURE 14 Same soldier as shown in Figure 13 4 years later (A) growth deformity of the head of the metatarsal has occurred on the injured side and (B) normal fifth metatarsal of opposite foot for comparison (See also Figure 15)

Schatzki None This is a 7 year old child who at the age of 2½ years had run out into the cold and had been exposed to a temperature below zero for 2 hours Severe blistering of the whole hand in a glove fashion developed

Fremont Smith Both hands?

Schatzki No only the right hand Her left hand was in a pocket when she was found About 1 year later a shortening of the fingers



FIGURE 15 Same soldier as shown in Figure 13 (*A*) growth disturbances of the head of the fifth metatarsal are seen in a lateral projection and (*B*) normal metatarsophalangeal joint for comparison

of the right hand was noted Here at the age of 7 the third fourth and fifth fingers are shorter than on the normal side Several phalangeal epiphyses are absent on the injured side In addition the joint surfaces of several interphalangeal joints showed punched out defects All this followed a 2 hour exposure to cold

Conn Possible

Schatzki Finally we saw very minor late cortical defects in two soldiers They are obviously not clinically significant but are conceivably of theoretical interest (Figures 17 and 18)



FIGURE 16 Growth disturbance and articular changes in a child Involved are the third fourth and fifth fingers of the right hand Reprinted by permission from Dreyfuss J R and Glimcher M J Epiphyseal injury following frostbite *New England J Med* 253 1065 (1955)

In summary, osteoporosis although frequently seen in the early *stages of frostbite, played no important clinical role It probably* was not caused by direct frost injury but apparently by disuse

New bone formation was rare Its significance is questionable Of course it is a sign of viability and may, therefore, be helpful when the question of amputation arises The changes which interested us most were the late joint changes which occurred in a *fairly high percentage in 15 out of 100 soldiers*

Horvath Were these 15 the more severely injured soldiers?

Schatzki I think they were not

Blair No they were among the less severely injured I do not know whether Dr Schatzki wants to make a point of it or not but I think on the subject of trauma the high predominance of joint changes in the eleven hand cases is interesting In how many of the eleven was it?

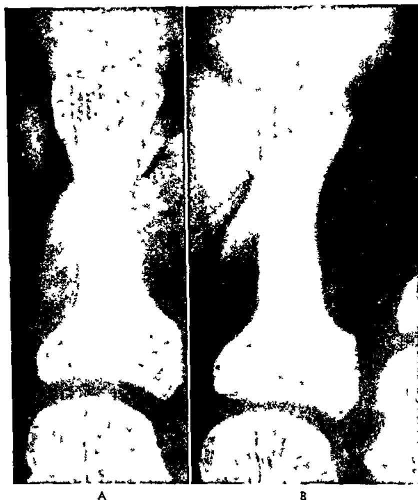


FIGURE 17. Late cortical change occurring outside the joint. (*A*) no abnormality is seen 6 months after frostbite and (*B*) localized cortical defect with bone reaction visible 4 years after frostbite.

Schatzki. Four out of eleven.

Blair. It is a much higher percentage than occurred in the foot cases.

Travell. Were the injuries to the hands more severe than to the feet on the average?

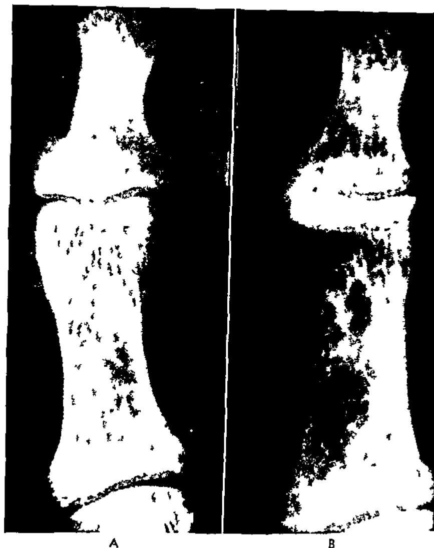


Figure 18 Late development of cortical defect outside the joint (*A*) the defect is not visible one year after frostbite but is clearly seen 3 years after frostbite (*B*) *This patient also had involvement of other joints The cortical lesions of this* patient and of the preceding patient are very similar to the joint lesions

Blair If so only slightly Among the hand cases there were two fourth degree cold injuries but there were also some mild hand cases in which there was no tissue loss

Schatzki Joint changes frequently occurred in persons who did not lose a single phalanx from the cold injury

Blair One that showed the most striking joint changes was only a second degree cold injury

Schatzki I was interested in the discussion of "the ill defined condition of the feet" and trench foot in relation to frostbite and in Dr Fremont Smith s remarks as to whether these were not actually the same things in a different degree I would like to know if patients with trench foot particularly with severe trench foot showed similar joint changes If not this may be of considerable differential diagnostic and theoretical interest

Montgomery You did not make roentgenograms of the cases classified as "ill defined condition of the feet

Schatzki In this group there were only two with so-called ill defined condition of the feet" and none of those showed joint changes

Fremont Smith What about immersion foot? Are there joint changes in immersion foot?

Schatzki I do not know of any roentgenologic studies on immersion foot They would be interesting Dr Simeone and I have discussed this There are many cases of trench foot in his group and it may be of value to study them radiologically

Fremont Smith There could be some follow up on some of the immersion foot cases of the war too

Simeone It would be very easy to do such a follow up We did not do it in our study because we had the impression that roentgenologic examination of the feet after cold injury showed only osteoporosis The pictures that I can recall did not show these cystic juxta articular changes but they were made within the first few months after the injury This was in trench foot

Fremont Smith Are immersion foot and trench foot more or less synonymous?

Simeone Yes I consider them so but I do not believe there is general agreement on this point

Behnke In patients who showed no joint or bone changes would you say that the circulation to the bones was normal?

Schatzki I have no way of telling Colonel Blair perhaps can answer that better than I

Blair I do not believe I can answer that quantitatively Captain Behnke The striking thing in these patients is the exceptionally good circulation that they do have as relates to foot warmth pulses and so forth but as to correlation of circulatory status with roentgenologic findings I cannot provide that information

Behnke It is rather disappointing, isn't it, that with the bone and joint changes the roentgenogram does not show more with reference to diagnosis and prognosis of the basic lesion? In the individuals who had symptoms, how many showed joint and bone changes?

Blair In the large group of third degree injuries, of which 35 cases were examined, 7, or 20 per cent, showed loss of joint mobility, and 28, or 80 per cent, showed no loss in joint mobility

Behnke I would like to ask one rather delayed question about symptomatology with reference to a sensation of abnormal warmth or burning Cold feet was mentioned In immersion and trench foot, paresthesia, in the form of abnormal warmth and burning is an outstanding sensation is it not?

Blair Yes, that is true We asked in the history and questionnaire forms questions as to paresthesia, consisting of burning tingling, and throbbing sensations In a fairly large group of the patients, particularly during the winter, there were complaints of burning and tingling, ranging from 39 per cent showing burning sensations, 44 per cent showing tingling sensations, and numbness in 75 per cent It is indeed a striking number that show paresthesia, occurring more in the winter months than during the summer months

Behnke Were the symptoms associated with erythema?

Blair This was very difficult to analyze because of the conditions under which the feet were examined, as I said before If there had been standard examination conditions, abnormal color could be evaluated, but many of the men did have erythema and color changes

Behnke I would like to ask Dr Shumacker whether or not, with reference to the erythema described, there is a big difference between frostbite and trench foot?

Shumacker I do not know that I can answer your question with accuracy because I must depend upon my memory and upon clinical impressions rather than upon detailed studies It is my impression that the feeling of abnormal warmth, both in trench foot and in frostbite, is usually of rather brief duration and occurs shortly after the period of rewarming begins, and that ultimately in trench foot, as in frostbite abnormal sensations of temperature are highly weighted on the side of a tendency to increased coldness, particularly on exposure to cold

I think perhaps Dr Simeone has more detailed information about this point but there is a high percentage of patients who for a long time after having sustained trench foot have feet that are abnormally sensitive to cold just as was true in Colonel Blair's group with frostbite

Fremont Smith Did you answer the question about color? Captain Behnke asked about color changes

Shumacker The same holds true with color During the period of reactive hyperemia shortly after injury the extremities tend not only to be warm but erythematous and subsequently the most common change is one of coldness and pallor particularly under the stimulus of exposure to a cool atmosphere

Fremont Smith Is that color change more prominent in trench foot and immersion foot than it is in frostbite or would it be about the same?

Shumacker I would say that it would be about the same

Montgomery Ungley and Blackwood (7) showed in a large series of immersion foot cases that a few hours or several days after [illegible] 10 weeks in which there is [illegible] the skin being red hot and [illegible] between this and frostbite is that the severely frostbitten area has lost its blood supply and the less affected portions just above the frostbitten area are small and are considered as lines of demarcation These narrow areas are inflamed for weeks and are often infected

Fremont Smith That is a very good point

Simeone These color changes which we describe as an inflammatory reaction do last for as much as from 4 to 6 months in the very severe cases Some of the patients even when lying in a horizontal position that late after injury may exhibit red dry somewhat edematous skin and even in the absence of gangrene or loss of part

Fremont Smith You attribute that to inflammation? You say inflammatory What do you mean by that infection?

Simeone No

Fremont Smith You mean tissue reactivity something distinct from vasomotor?

Simeone Presumably the arterioles and capillaries are more dilated than they normally are

Fremont Smith It was your phrase inflammatory which I did not know how to evaluate

Simeone I would take it as a chemical inflammation rather than a bacterial inflammation that is a reaction to the exposure to cold Whether it represents the result of direct injury to the affected cells or an indirect injury resulting from prolonged anoxia and ischemia I do not know

Fremont Smith You do not think it is caused secondarily by vascular changes?

Simeone I do not know that even It could be

Fremont Smith From your point of view it could be all secondary to the vasomotor changes?

Montgomery No it is easily demonstrated at least in immersion foot that there are very marked histologic changes certainly in muscle and nerve

Fremont Smith Lasting several months?

Montgomery Yes

Shumacker Dr Montgomery was referring to the greater extent of involvement in what we know as immersion foot in contradistinction to trench foot I have always considered this to be a rather prominent point of distinction between these two types of cold injury With reference to the greater extent of injury in immersion foot it is of interest that large nerves are frequently paralyzed in this condition The peroneal nerve for example is completely paralyzed in a significant percentage of cases of immersion foot while in contrast any nerve injury that is demonstrable in trench foot is usually manifested simply by scattered areas of hyperesthesia or hypesthesia I believe that no one saw patients with trench foot during World War II who had paralysis of a major peripheral nerve but major peripheral nerve paralysis was noted not infrequently in cases of immersion foot

Fremont Smith And that was not from mechanical pressure against the nerve?

Shumacker Not so far as one could tell

Montgomery The distinction is not a real one It is a question of area or volume involved In immersion foot the foot and leg are usually severely chilled in frostbite of the lower extremity the foot alone

Shumacker I agree with that

Simeone Another interesting phenomenon during this late "inflammatory" phase in relation to the complaint of heat which Captain Behnke mentioned is the subjective sensation of heat alternating with one of cold This occurs particularly during the night and in the absence of visible objective changes

Fremont-Smith Have any skin temperature changes been taken during those fluctuations?

Simeone Not that I know of, as actual measurements, but by palpation no obvious changes in the skin temperature have been felt coinciding with the subjective sensations

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EXPERIMENTAL COLD INJURY IN THE RABBIT

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I WOULD LIKE TO PRESENT the experimental method and background for the animal studies that Dr Schatzki and Dr Kulka will subsequently present In this study we tried to reproduce as closely as possible in animals the cold injury lesions of soldiers that have been described previously

We devised a method of producing experimental ground type frostbite in rabbits Adult New Zealand white rabbits were prepared in a standard manner the rear feet were clipped and depilated with a depilatory cream as seen in Figure 19

We then took the rabbit and placed him in the apparatus shown in Figure 20 our so called rabbit foxhole We endeavored to simulate the soldiers conditions of freezing first as to ambient temperature −25°C second as to similar exposure time about 4 hours third as to immobility and fourth as to dependency

We insulated one foot to protect it against any cold injury so that it might serve as a normal control for all histologic and roentgenologic studies I would like to point out that in trying to produce this model of human ground type frostbite there are several distinct differences between rabbit and human cold injury One difference is that the rabbit foot (Figure 19) is largely skin overlying skeleton There is very little soft tissue in the rabbit foot as compared to the human foot The second difference was pointed out to us by Dr Montgomery s group He made a very helpful suggestion and we plan to use it The soldier standing in the foxhole is in a state of weight bearing Throughout the period of cold exposure his proprioceptive mechanisms are being stimulated and he also has the opportunity of tensing his muscles These animals with their legs in a freely dependent position differ in these respects from human frostbite Dr Montgomery suggested that we might put a block under the two rear feet so that they would be in contact in order that they would have a weight bearing sensa



FIGURE 19 Hind feet of rabbit depilated before freezing

tion and muscle tensing ability similar to human feet Dr Kulka and his group are using this modification in some of the freezing experiments they are undertaking

We placed the rabbit in the foxhole and put an electric heating jacket about him to maintain his rectal temperature at 38.3°C plus or minus ½°C Then we placed thermocouples on the toes and dorsum of both feet to measure the place and time when skin temperature dropped to a point where freezing begins By timing with a stopwatch from the moment when freezing began, we were able to control the degree and extent of injury A one minute freeze, in our experience, will produce a very mild cold injury, 20 minutes of freezing time produce a mild to moderate fourth degree injury forty minutes produce a very severe injury which



Figure 20. Apparatus for producing experimental frostbite in the rabbit.

invariably causes loss of all phalanges. Total cold exposure averaged about 4 hours.

Fremont-Smith: These rabbits are without anesthesia?

Blair: These are totally without anesthesia of any kind. They are prepared as in Figure 20 and placed in a deep-freeze unit which is kept at −25°C. The shortest period of time in which we have had a rabbit freeze is 62 minutes. Some have remained in the deep freeze for 24 hours without freezing, and we had to remove them because their resistance to cold was so great that they did not freeze.

Fremont-Smith: I think the individual variation is interesting.

Blair: It is interesting and we see the same thing in human beings. One man will get severe frostbite while standing in a foxhole while his buddy who is standing next to him and wearing the same clothing may get no cold injury at all.

Figure 21 shows a lesion one day after cold injury, with the left foot uninjured because it was insulated, and the frostbitten right foot in the stage of swelling or hyperemia.

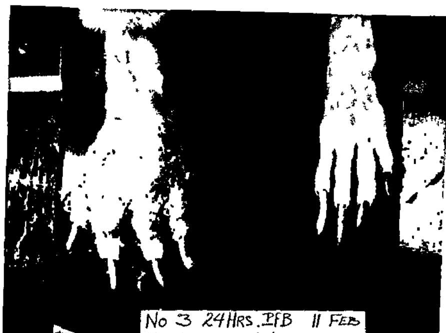


FIGURE 21 Frostbite lesion one day after freezing (left foot uninjured as control)

Figure 22 shows the onset of gangrene occurring on the seventh day in the right foot, with the normal control foot on the left This is a 20 minute freezing animal, which eventually lost its terminal phalanges on the right foot

The third difference between rabbit lesions and human lesions is the definite icing of the tissues in all fourth degree frostbite in the rabbit This goes back to the point that Dr Fuhrman brought up We do not see icing of tissues too often in human cases, but it is an universal occurrence in rabbit lesions

That is a very brief summary of the cold injury that we produced in animals, which Dr Schatzki and Dr Kulka will discuss in more detail later

Simeone Did those animals form blisters?

Blair Yes these animals do form blisters, but they are not as large as those you see in humans We can delimit or, shall we say, telescope this injury by using another method of depilation which Figure 23 shows The rabbit is depilated only to the base of his phalanges This tends to telescope the injury so that we see severe to very mild injury over a much smaller area There are intact

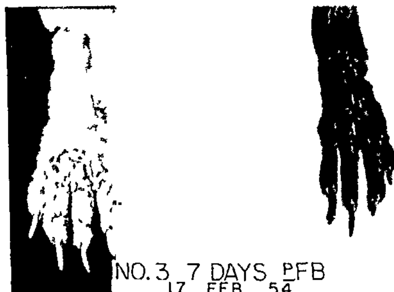


FIGURE 2[illegible] Frostbite lesion one week after freezing (left foot uninjured as control)

blisters throughout this area They are not as large as we see in the human cases but they definitely occur

Another reason that blisters are hard to observe is that once the animal is put back into his cage blisters are almost always broken and are no longer present The photograph in Figure 23 is about 6 hours after thawing has occurred

Burton If you took an animal down almost to the freezing point and kept him for many hours not quite freezing would there be any injury?

Blair This is one thing that we have not done and I do not know whether we could because the skin goes down to a critical temperature and then either freezes or spontaneously rewarms I know of no method by which the animal can be taken down to the critical temperature and held there indefinitely

Burton I thought perhaps you might have done that in some of these animals that were so resistant that you eventually gave up Did you ever see any injury in them? They are animals that did not quite get down to freezing aren t they?

Kulka They didn t show much external evidence of injury and unfortunately we have not done microscopic studies on many of these animals In some instances they did show bone necrosis



FIGURE 23 Blister formation in experimental frostbite

Burton Evidently freezing is not absolutely essential to bring about these pathologic changes

Kulka We cannot be sure about that point as yet, because in these particular animals we did not have thermocouples at the tips of all toes

Blair We had thermocouples on one toe of each foot Of course, on the tip of a toe there might have been some freezing in an area away from the thermocouple If we could bring skin temperatures down and hold them just above freezing that would answer Dr

Burton's question, but we have not been able to devise a method of doing it

Burton Perhaps you could immerse them in a thermostated water bath

Kulka We thought we might inhibit peripheral vasodilatation by cooling the body and we thought we might prevent freezing by raising the ambient temperature to 0°C This is one method by which we are planning to study the point you are interested in

Montgomery Dr Burton, if the temperature of the rabbit's leg is kept slightly above zero, by cold water for 4 hours, there will be demonstrable histologic changes in some of the fibers of nerve and muscle, and on rewarming some neuromuscular dysfunction persists

Hedblom Was it in an effort to make the rabbit experiment simulate the military situation that you allowed the animals to rewarm slowly at room temperature? Or did you also rewarm some of these rapidly?

Blair We were not going to report our data on slow and rapid rewarming because it is now in the process of being analyzed We did use this method of producing frostbite and tried to evaluate rapid rewarming room rewarming, and delayed rewarming in these particular animals, but the only thing we can say definitely from the status of our data at the present time is that we have not been able to reproduce the dramatic benefit of rapid rewarming on immersion produced frostbite

Hedblom On the immersion?

Blair On immersion frostbite, yes where animals are frozen very rapidly by immersion in a freezing bath This work is very similar to the studies of Dr Shumacker (1), Dr Crismon (2), and Colonel Lewis (3) at Randolph Air Force Base These men are completely in agreement as to the benefits of rapid rewarming There is no doubt as to the excellent results of rapidly rewarming immersion-produced frostbite

Fremont Smith Does that apply only to regular frostbite or what you called immersion frostbite which is a new combination of words from what we have had previously in this discussion?

Shumacker Some of my associates and I (4) did expose unanesthetized mice to a low ambient temperature and thus produced freezing of the tails In these animals rapid rewarming of the frozen tails very dramatically effected a great saving of tissue

Admittedly the mouse's tail is not entirely comparable to the rabbit's foot

Blair Our own data have not been worked up and analyzed sufficiently to draw definite conclusions, so we cannot say as yet that rapid rewarming has not been beneficial, but we have not seen any such dramatic results in any of our animals from rapid rewarming that you see when you freeze by immersion in alcohol cooled by dry ice and then rapidly thawed

Montgomery Colonel Blair, did you freeze any of the animals for as short a time as the "immersion type' of frostbite?

Blair No, we froze ours to what we call a very mild fourth degree injury, produced by one minute freezing exposure, but the total exposure time ran 4 to 6 hours in the cold

Montgomery May the beneficial effect of rewarming apply solely to the frostbite that results from brief exposures to severe cold?

Blair That is our current trend of thinking especially, for example, in high altitude frostbite which usually occurs very quickly

Montgomery We know that the severity of frostbite is closely related to the duration of freezing, at least up to a half hour or more At high altitude, in liquid gases, in cold brine, or with a cold rod, tissue can be frozen in a minute or so If the freezing element is removed at the end of that minute and the part is left at room temperature, the tissue may not thaw for many minutes However, if the part is rapidly rewarmed in warm water it may thaw in a minute, and the duration of freezing has been greatly decreased This seems to me the explanation for the success of rewarming in the case of freezing of short duration and its failure in the case of prolonged freezing

Blair If you assume that these animals are relatively ischemic from the time that they are exposed to the cold or from when spontaneous rewarming fails the total time that they are ischemic is not appreciably affected in our type of experiment by rapid rewarming as is the case when they are put into a brine bath for 3 minutes and then rewarmed in 2 minutes, a total period of ischemia or frozen state of only 5 minutes

In our case, where we have measured actual freezing for 20 or 40 minutes and then rewarmed in 2 minutes, the total period of ice formation or of complete ischemia is many times that found in the immersion type of freeze injury

Horvath You are saying basically that what the Germans found is what you have found, that the longer the period of exposure the slower the rewarming should be to be more effective?

Blair That is quite true.

Horvath So if there is a long period of exposure, then the rewarming should be slow. If the cooling has been very rapid, then the rewarming is correspondingly rapid.

Fremont-Smith And this would apply then to total time of exposure to severe cold and not limited to the time of actual freezing?

Horvath I think it would be a combination of temperature and time of exposure. I do not believe the temperature factor could be eliminated.

Fremont-Smith Surely, but I meant if there were 4 hours of quite severe cold and then 20 minutes of freezing of tissues, it is the total period of time that is involved here, not the 20 minutes of freezing alone.

Horvath Yes, I would say roughly that is so.

Shumacker Colonel Blair, do you mean that you gained the impression from this particular experiment that rapid rewarming of the limbs increased the tissue loss?

Blair No.

Shumacker Then the point made is not true, because if the thesis were correct, one would expect dramatic improvement in survival of tissue when the frozen limbs are allowed to thaw spontaneously and thus to take a longer period of time.

Blair But the point is this, Dr. Shumacker. What I think is that after a period of time during which the part has been frozen, say, for a total period of 40 minutes, then whether it is rapidly or slowly rewarmed apparently has little effect on tissue loss. On the other hand, if the icing has occurred only for a period of 2 minutes and then it is thawed in 2 minutes, there is a very dramatic effect, because 30 or 40 minutes would be required to room thaw, and you are therefore comparing 4 minutes of frozen state with 35 or 40 minutes in the frozen state.

Shumacker What you are saying, Colonel Blair, is that in these experiments you did not find rapid warming of benefit, but you are also stating that you obtained no evidence that slow rewarming was of benefit.

Blair That is quite right except from this standpoint Many clinicians have said that when a frostbitten part is rapidly rewarmed greater edema is produced greater pain and discomfort to the individual and the clinical response from the standpoint of symptoms is poorer with rapid rewarming than with ordinary spontaneous rewarming at room temperature

Shumacker But those are mostly uncontrolled observations and I could cite other clinical studies from which the opposite conclusions were drawn For example those made by Jack Adams Ray and his associates (5) during a severe Stockholm freeze You will recall that they studied 100 or more cases at that time and felt that the damage was decidedly less in the group of individuals who had brought about as rapid rewarming of the cold injured part as was possible under the circumstances

Montgomery I wonder if there are any controlled experiments which would show that rapid rewarming has any advantage other than that it shortens the length of time in which the tissue is severely chilled

Fuhrman I think I can answer that There was a set of observations reported by Hardenbergh and Dawson (6) They kept the rabbits feet frozen in the group which were to be rapidly rewarmed for the same length of time as those thawed in air and still they got better tissue survival

Blair Up to what limit? They used an immersion freezing quick freeze

Fuhrman They used an immersion freeze of something like 30 minutes I do not recall the exact figures but those that thawed in air took 18 minutes to thaw so they kept the others frozen 18 extra minutes and then rapidly warmed them

We attempted to get at the same thing in another way The temperature at which the foot is rewarmed is critical as Dr Shumacker found and as we did also Thawing temperatures of say about 25°C in water are much less satisfactory than 42°C in water

Blair We used 42°C in our particular observations

Fuhrman Yet the time it takes to thaw in water at 42°C is almost identical with the time that it takes to thaw in water at 25°C We have some measurements of that in which we put subcutaneous thermocouples in feet, froze them and then put one group in water at 25°C and another group in water at 42°C There is only about one second s difference in the total time that

the foot is below 0°C, and yet there is much better tissue survival in those thawed in water at 42°C than those in water at 25°C. So there is something more than simply a reduction in time that the ice is present in the tissue.

Montgomery I think that is very helpful but I think it is also wise to remember that some tissue such as human skin can stand from 15 to 20 minutes of what is ordinarily called frostbite without having any permanent damage.

Fuhrman Yes I think the same thing should be repeated keeping the foot frozen for say 3 hours or something of that sort and then rapidly warming it.

Behnke Was deep body temperature recorded in these animals?

Blair Yes on all of these animals we had a colonic thermocouple and during the freezing process we kept the deep body temperature at 38°C. After we took them out of the freezing box the body temperature during thawing would usually rise to 39.3° or 39.5°C. We had records of the deep body temperature throughout the experiment and in almost every case there was no later hypothermia. On the other hand deep body temperature usually goes up to normal or higher than normal.

Behnke Concerning rapid rewarming the point that I would like to make is the deep body temperature is elevated and the peripheral part is not rewarmed. It may be that one of the benefits from rapid rewarming is the elevation of deep body temperatures which in turn has a beneficial action in increasing circulation to the extremities a much better blood flow is the result of elevation of deep body temperature.

Blair Of course many people have suggested a very plausible experiment and that is of thawing by means of diathermy rather than by just rewarming the periphery as in warm water immersion.

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ROENTGENOLOGIC CHANGES IN FROSTBITTEN RABBITS

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IN GENERAL, we tried to obtain early, intermediate and late roentgenograms on the frostbitten rabbits, but a rigid schedule was not adhered to. Because of inadequate help and other factors roentgenograms were made of some rabbits only in early stages and of others only in later stages.

The rabbits showed roentgenologic changes which in some respects were similar to and in others different from those seen in frostbitten humans. Roentgenologic examinations were performed on 73 rabbits. Practically all of them showed loss of phalanges. Sometimes they broke off just where the soft tissue ended, as Figure 24 shows, and Dr. Kulka found in some of them granulations which were actually growing into the bone at this level. Whether that was always so I do not know.

The extreme frequency of periosteal new bone formation was interesting. As we said previously, of the 100 soldiers only two showed some new bone formation and only in a very minor degree. Of the rabbits which were examined, 82 per cent showed new bone formation, and I am fairly certain that if we had made roentgenograms of them more frequently, especially between 1 and 2 months following exposure, all of the rabbits, or practically all of them, would have shown new bone formation at one time or another.

The degree of new bone formation varied considerably. Figure 25(A) shows new bone formation 13 days after the frostbite. (The earliest new bone formation which we saw in any case occurred 6 days after frostbite.) Figure 25(B) shows that new bone has increased 47 days post frostbite, and has almost disappeared 4 months after the exposure (Figure 25(C)).

At times this new bone formation was very marked, as the next case shows. Seven days after the frostbite there is no new bone formation (Figure 26(A)). Figure 26(B) is 23 days after frostbite

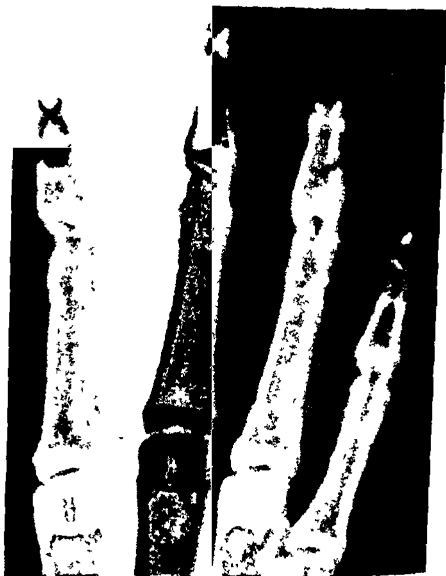


FIGURE 24 Rabbit No 66 Destruction of exposed phalanges, also new bone formation is visible 1½ months after frostbite

and quite extensive new bone formation is shown Forty four days after the frostbite, the new bone formation increased [Figure 27(A)] It is quite different from the new bone formation that we saw in humans It looks more like the massive new bone formation which one may see in scurvy caused by periosteal hemorrhage but

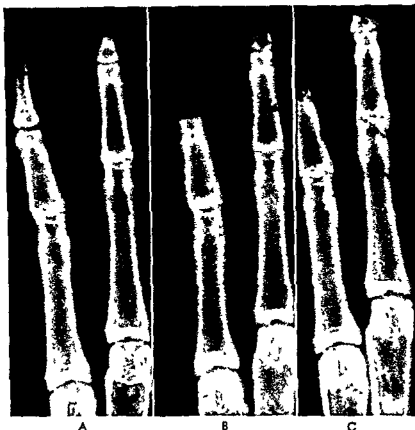


FIGURE 25 Rabbit No 31 Early new bone formation of second toe (*A*) 13 days, (*B*) 1½ months and (*C*) 4 months after frostbite Early new bone formation is visible on (*A*) it is more obvious on (*B*) and has almost disappeared on (*C*)

that was not the cause, as the pathologic specimens will show Six months after the frostbite, some of the new bone formation become consolidated in some places and practically disappeared in others [Figure 27(*B*)]

Figure 25 shows when new bone formation was first noted Each animal is charted only once namely at the time when the new bone formation was first noted If new previous post frostbite roentgenograms had been taken in the animal this was indicated by the symbol 0 If previous post frostbite films had been made



FIGURE 26 Rabbit No 66 Development of new bone formation and osteoporosis (*A*) bones appear normal 7 days after frostbite (*B*) new bone formation is present about the second and third toes 23 days after frostbite (See Figure 27)



FIGURE 27 Rabbit No 66 (*A*) New bone formation is visible about the proximal phalanges of all toes 1½ months after frostbite (*B*) It has become well delineated after 6 months (*B*) also shows osteoporosis and extensive destruction of the terminal phalanges

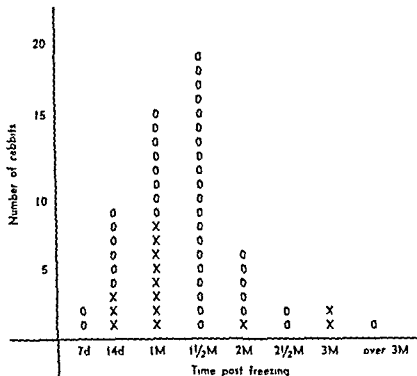


Figure 28. Time of first occurrence of new bone. O is a rabbit with no previous films. X is a rabbit with previous films showing no new bone. Total 58 animals.

of the rabbit which had not shown new bone, this was indicated by the symbol X.

Most rabbits showed new bone first around 1 to 1½ months following the frostbite. The greater number of them, however, had not had any previous post frostbite roentgenograms and it is therefore quite possible that the new bone formation occurred somewhat earlier.

In two animals the new bone was not noted until 3 months post frostbite although they had had earlier post frostbite roentgenograms.

Horvath: How long before that? The first one was taken when, 14 days, 2 months later?

Schatzki: They had been taken 14 days and 23 days, respectively, after the frostbite.

Horvath If they were taken 2 days or a week before the 3 months then it would be significant but this way it may not be

Schatzki I agree

Blair If you can give me the number of the animal I can give it to you I have all the dates of the roentgenograms on each animal

Fremont Smith The roentgenograms were taken serially?

Blair Roughly about a month apart but as I said we had trouble with change of technicians and there are some gaps where we had no roentgen ray technician available to make the films

Talbott Were the animals given antibiotics routinely?

Blair No they were not given antibiotics at all

Talbott There was no specific drug therapy throughout the period of study?

Blair No

Schatzki Figure 29 shows how high the percentage of the animals was at any given time which when roentgenograms were made at that particular time would show new bone formation Almost all the animals which were examined between 1 and 2 months after exposure showed new bone formation

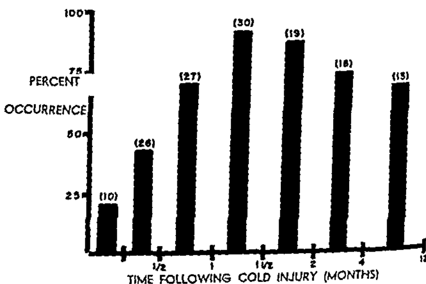


FIGURE 29 Rabbit periosteal new bone Figures in parentheses ( ) represent numbers of observations within time interval indicated

Figure 30 shows the distance of the new bone formation from the nearest phalanx exposed to air as a result of overlying soft tissue loss. About 50 per cent of the areas of new bone formation when first seen were in a phalanx which was partially exposed to the air as a result of soft tissue loss. The first appearance of new bone decreased with the increased distance from the air exposed phalanx. In six instances, however, new bone formation was seen in apparently intact digits.

In later weeks the new bone gradually decreased in amount. The nine animals who had shown new bone formation and were re-examined 5 to 12 months following frostbite all showed regression or disappearance of the newly formed bone. In the majority the new bone had completely disappeared. The others showed regression of new bone by that time.

Montgomery The bone was there but it was not forming new bone at that time? You say "regression" not resorption?

Schatzki Let us say there was less new bone there than there had been at the previous examination of the same animal.

Montgomery Less formation?

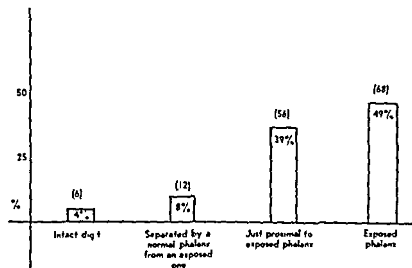


FIGURE 30. Location of new bone in regard to exposure. Figures in parentheses ( ) give number of phalanges with new bone. Each phalanx appears only once, when new bone is first seen.

Horvath If they were taken 2 days or a week before the 3 months, then it would be significant, but this way it may not be

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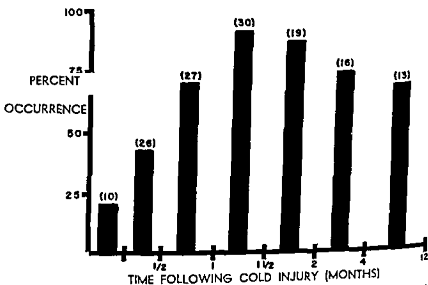


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Montgomery: The bone was there but it was not forming new bone at that time? You say "regression," not resorption?

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Montgomery: Less formation?

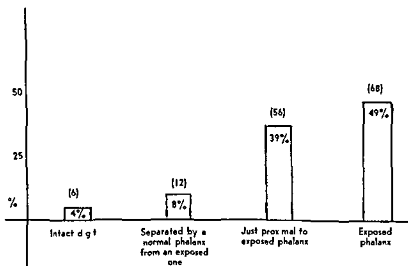


FIGURE 30. Location of new bone in regard to exposure. Figures in parentheses ( ) give number of phalanges with new bone. Each phalanx appears only once when new bone is first seen.

Schatzki No, the actual new bone had regressed compared with the previous examination

Montgomery Resorbed?

Schatzki Resorbed, whatever that mechanism is The new bone usually looked different from that seen in humans Our two human cases and the few cases which have been described in the literature showed thin laminated periosteal new bone formation whereas the rabbits usually had big masses of new bone

The second most common change which we saw in these rabbits was decalcification of bone Very little decalcification was recognizable early after the frostbite, quite in contrast to the human cases But as the animals became older, it became quite obvious that they did show very marked demineralization in other words at a time when the humans did not show such changes

Figure 31(*A*) shows a normal rabbit foot before frostbite, Figure

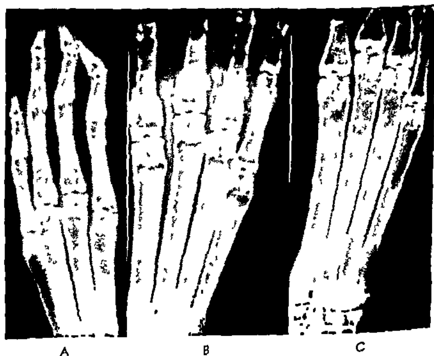


FIGURE 31 Rabbit No 75 Development of osteoporosis (*A*) before frostbite (*B*) 1 month after frostbite with questionable early osteoporosis and marked new bone formation and (*C*) marked osteoporosis of the metatarsals 5 months after frostbite

31(*B*) was taken one month after the frostbite, and Figure 31(*C*) 5 months after frostbite There is questionable slight decalcification 1 month after frostbite Five months after frostbite it is quite obvious The change is quite marked, and not a result of different technique Something has been eaten away When the thickness of the cortex of the third metatarsal is compared at the different dates, the marked change can be noticed Because of the eating away of the cortex, the metatarsal has developed a waistline

Figure 32 is another case showing the marked demineralization of the bones with irregular cortical thinning 5 months after the frostbite The thinning may not only occur from the outside but also from the inside, resulting in widening of the narrow cavity All these changes do not look in any way different from severe osteoporosis which may occur in humans in cases of disuse, for instance, in a limb that has been in a cast for several weeks Whether the mechanism is the same is, however, open to question The pathologic studies of Dr Kulka seem to indicate that it is not

The "osteoporosis" was not visible before the first month It became increasingly noticeable when roentgenograms were made of the animals at a later date, so that of the rabbits with roentgenologic examinations between 4 and 12 months following frostbite over 75 per cent showed it

We were, of course, very anxious to find if we could see joint changes in these animals We did not see anything which was comparable to the juxta articular changes in humans There was only one case which definitely showed joint changes The proximal interphalangeal joint of the third toe was markedly destroyed (Figure 33) There was marked localized soft tissue swelling present, and later ankylosis of the joint occurred

This looks so much like a septic joint in humans that I cannot help but feel that it actually was a septic joint, although the pathologic specimens, Dr Kulka tells me, were really amazingly free of evidence of infection This particular joint when seen later at post mortem showed ankylosis and at that time no evidence of infection In none of the rabbits did we recognize the cystic, punched out juxta articular defects which we had found in humans

To summarize the roentgenologic appearance in the rabbits, there were two aspects which were strikingly different from the human frostbite One was the high incidence of new bone formation and the other was the late change of the bone which looked like osteoporosis

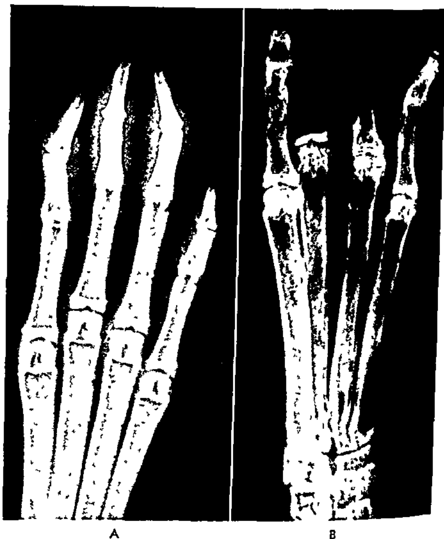


FIGURE 32 Development of marked osteoporosis of rabbit No 59 (*A*) before frostbite and (*B*) 5 months after frostbite

Talbott Did it appear that as the periosteal proliferation increased, the osteoporosis began to appear? I did not see periosteal proliferation in any of your figures which you have shown on osteoporosis

Schatzki Yes, there were a number that showed both together



FIGURE 33 Rabbit No 33 (A) Destruction of proximal interphalangeal joint followed later (B) by ankylosis This is the only rabbit joint in which destruction was found It was not likely caused by infection and not comparable to the joint changes which were seen in man

Hedblom I notice a very interesting thing Did you happen to observe in a greater or lesser degree in every one of them that the toes on the outside were better preserved than the ones on the inside?

Schatzki I think that is correct

Hedblom They would have cooled off more rapidly They would also have warmed up more rapidly

Schatzki I talked that over with Colonel Blair and Dr Kulka and we have an explanation for that

Blair Dr Kulka will probably have something further to say on it But one thing you must realize is that the middle two toes stick out very far, quite a bit farther than the ones on the side That is not only related to their cold exposure but when they walk around, so far as trauma is concerned, those two protruding middle toes probably take the brunt of the trauma to the rabbits' feet after cold injury

Hedblom That would explain it, perhaps

Blair You will also notice that they tend to lose those particular toes later

Hedblom Just as we get most of our destruction to the great toe and the fifth toe where we have the greatest pressure and trauma

Blair Yes, I think that is a fact Possibly Dr Kulka has some other suggestions to make

Kulka We have wondered on the basis of arterial injection studies, whether the blood supply to the fifth toe might be more anastomotic than that of the other toes but, as yet, we cannot be sure The fact is that the fifth toe in the rabbit is less susceptible to frostbite gangrene under the conditions of our experiments

HISTOPATHOLOGIC STUDIES IN FROSTBITTEN RABBITS

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IN ATTEMPTING TO DETERMINE the sequence of events which lead to tissue damage in frostbite, the pathologist has been faced with two major difficulties (1) The difficulty of obtaining histologic material from human lesions of varying intensity in various stages of development, and (2) the lack of an experimental model which duplicates the condition under which human frostbite commonly occurs I mention the first of these difficulties in the hope that more human material may be collected in the future Medical examiners in particular, are in a position to be of help

With regard to the second difficulty the technique developed by Colonel Blair represents a significant advance The studies which I shall present are concerned primarily with the experimental lesions produced by this technique* Such lesions show a progressive decrease in intensity of injury from the distal most portion of the digit proximally Thus there is a possibility of distinguishing between different mechanisms of tissue injury which might be active at different degrees of cold exposure

We examined about 30 lesions which ranged in duration from 38 minutes to 333 days after the animal was removed from the freezer Our findings indicate that each individual tissue reacts differently to freezing injury The lesions of arteries bone, and subcutaneous connective tissue serve to illustrate three distinct mechanisms of necrosis

The arterial lesions will be described first because of their possible effect on blood flow to the other tissues This type of lesion

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*These studies were carried out in the Departments of Physiology and Pathology at Harvard Medical School under contract with the Research and Development Division Office of the Surgeon General Department of the Army (Contracts DA-49 007 MD-342 principal investigator Dr Eugene M Landis and DA 49 007 MD 645 principal investigator Dr Gustave J Dammin) The following members of the Laboratory staff aided significantly in the work of the project Cpl W F Straus M S Cpl E Gartner B S Pvt R A Wolbach Ph D Pfc T B Roos M S W Koehler M A and Miss Lenore McGaffey

is of particular interest because it is typically focal and therefore, difficult to explain either on the basis of a direct effect of cold on the tissue or on the basis of ischemia, which is the other pathogenic mechanism that is commonly invoked

Figure 34 shows an arterial lesion from a rabbit sacrificed 8 hours after a 12-hour exposure in the freezer A segment of the muscular media has undergone lytic necrosis, there is some neutrophil infiltration, and a mural thrombus has begun to form over the lesion Thrombosis of arteries was present as early as 3½ hours after removal from the freezer

Fremont-Smith Did you have serial sections of areas like that so that you could follow through on several segments and be quite sure that what you have is fairly characteristic of that lesion?

Kulka We have few serial sections but from having seen large numbers of longitudinal as well as cross sections of different arterial lesions, we believe that they are segmental or focal in character (Figures 55 58 and 59 on page 139)

I should also bring out the fact that the arterial lesions are quite irregular in distribution We often had to take several sections through a frostbitten digit to find a good example, but we found some evidence of focal arterial necrosis whenever the metatarsal thermocouple had indicated irreversible freezing, that is, −6°C

In later stages, some of these lesions may take on a curious similarity to the arteritis in systemic hypersensitivity Figure 35 shows an arterial lesion 8 days after freezing There is permeation of the arterial wall by a fibrin-like material, leukocytic infiltration and proliferation of endothelial cells

Either of two things may then happen to the artery It may become thrombosed (Figure 36) or it may undergo repair with intimal fibrosis (Figure 37)

FIGURE 34 Segmental arterial necrosis 8 hours after frostbite (hematoxylin eosin stain x185) Courtesy of the Armed Forces Institute of Pathology, Walter Reed Army Medical Center Washington D C

FIGURE 35 Arteritis 8 days after frostbite (hematoxylin eosin stain x190) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

FIGURE 36 Arteritis with thrombosis proximal to region of gangrene 4 days after frostbite (hematoxylin eosin stain, x98) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington, D C

FIGURE 37 Endarterial fibrosis and atrophy of skeletal muscle 90 days after frostbite (hematoxylin-eosin stain x100) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C



FIGURE 34



FIGURE 35



FIGURE 36



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Figure 34 Segmental arteri l necros s 8 hours after frostb sta n x185) Courtesy of the Armed Forces Institute of Pa Army Med cal Center Wash ngton D C

Figure 35 Arterit s 8 days after frostb te (Hematoxylin-eos n of the Armed Forces Inst tute of Pathology W lter Reed A Wa h ngton D C

Figure 36 Arterit s w th thrombos s proximal to region of g frostb te (hematoxylin eos n sta n x98) Courtesy of the Arm Pathology Walter Reed Army Med cal Center Washington D

Figure 37 Endarterial fibros s and atrophy of skeletal muscl b te (hematoxyl n eos n sta n x100) Co rtesy of the Arn Pathology Walter Reed Ar Med cal Center Wash ngton



Figure 34





Figure 36



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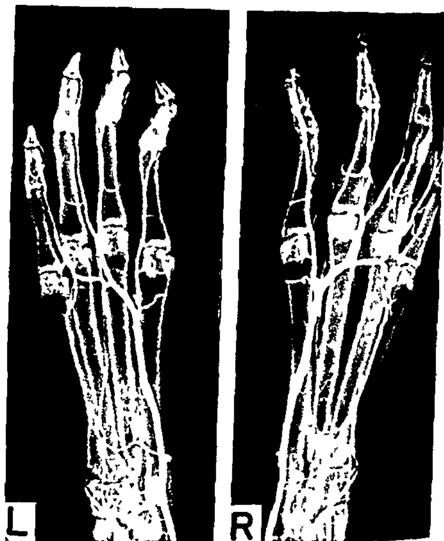


FIGURE 38 Post mortem arteriogram (barium sulphate gelatin mass) 5 days after frostbite The left foot was only lightly exposed and serves as a control. Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

you anticipated The skin temperatures of the other six rabbits' feet did not appear to differ significantly

Crismon Did you see any reasonable amount of increase of flow of the radio-opaque material over into the venous side in these?

Kulka Yes but as yet we have no quantitative data on this point

Burton Does that great increase of arterial supply look rather reminiscent of Paget's disease?

Kulka I do not know

Montgomery In Paget's disease the increased arterial supply is in the bone

Burton But the thin bones do not have an intrinsic supply, do they?

Kulka Dilatation of the arteries within the bones is seen

Burton Are there arteries in the bone?

Kulka Yes

Fremont-Smith Something must be reabsorbed around the arteries to allow them to enlarge in the bone

Kulka They may have enough room for expansion For instance, in the terminal phalanges the main artery runs up through the center of the medullary cavity (Figure 38)

Burton The one on the right is very easily visible

Kulka Yes, because there is arterial dilatation on the right (Figure 38)

Fremont-Smith You are sure that is inside? You cannot tell from this which plane that is in, but you know by the section that it is inside?

Kulka Yes, it is inside

Montgomery Is this dilatation of the main arteries limited closely to the point of the edge of the frostbitten tissue?

Kulka No It seems to extend proximally and we haven't determined its proximal boundary

Montgomery As you take sections along that, is the whole artery damaged?

Kulka The lesions tend to be segmental rather than diffuse

Fremont-Smith What about the foot that has not been exposed? Do you know whether that has these arterial dilatations?

Kulka No it does not You can see the control in Figure 38

Simeone Don't you think, Dr Kulka, that there may be dilatation of arterioles and other very small blood vessels which do not appear in the arteriograms but which cause a decreased peripheral resistance and an increased rate of blood flow through the large vessels which do appear in the arteriograms? The dilatation and tortuosity could then be related to that increased rate of blood flow as occurs elsewhere in the body under other circumstances



FIGURE 39 Post mortem arteriogram (barium sulphate gelatin mass) 18 days after frostbite Arterial dilatation is maximal Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C



FIGURE 40 *Post mortem arteriogram (barium sulphate gelatin mass) 59 days after frostbite Arterial dilatation persists and is associated with increased tortuosity* Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

Kulka I think that is very possible We made another observation which may have a bearing on this point About the same time that the arteries dilate, the gelatin mass which does not ordinarily penetrate capillaries appears in the veins in considerable quantity What may happen is indicated in Figure 41, which shows an arteriovenous anastomosis 4 days after exposure of the animal There is an artery leading into a wider vessel which has sphincter like concentrations of smooth muscle cells in its wall, as you follow this channel along it ends in a typical, thin-walled vein You will notice that the lumen is at no point narrower than it is in the arteriole itself Thus there appears to have been a complete arteriovenous shunt We were quite excited about this finding but disturbingly, the section came from one of the control feet Then I noticed that the bone in this digit was necrotic What apparently had happened was that despite the way we insulated the control foot this one received a sufficient cold exposure so that there was marked tissue damage and also, presumably, paralysis of the arteriovenous anastomoses

Blair This might answer Dr Montgomery's previous question of whether or not we see any cold injury in the periods of hunting in repeated hunting with supercooling This is a case where we could not diagnose the presence of cold injury by means of the temperature chart, but apparently it occurred during the cooling phases through the foot and involving the bone

Montgomery The trouble is, Dr Kulka did not have his thermocouple at the very tip of the toe so we cannot interpret it for sure

Burton You do not interpret the opening of shunts as pathologic do you? They open up as a normal physiologic function We know they are as large as 200 μ, because in shunts in other areas, Barlow (2) and Boyd (3) found beads of 200 μ coming through in the mesentery Are you interpreting the opening of that shunt as indicating a pathologic condition?

Kulka We do not know as yet I think it is going to be a quantitative matter There is evidence that in the dog's leg up to 30 per cent of the blood normally flows through arteriovenous anastomoses of a diameter greater than 40 μ (4), and this percentage is even greater in the paw If 90 per cent of the blood went through such shunts, a marked change in the circulatory pattern might result

Fremont Smith This would reduce peripheral resistance and reduce pressure in the artery and I cannot see why this in itself



FIGURE 41 Arteriovenous anastomosis 4 days after frostbite Arrows in lumen indicate direction of blood flow (hematoxylin eosin stain x250) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

should lead to either dilatation or elongation of the arteries back of the shunt I would think if anything it would put less pressure on them because the one way that peripheral resistance can be reduced is to dilate the arterioles or open up the shunts so I should find it difficult to see how this alone the mere opening of shunts, would have any effect in dilating the arterial tree or elongating it

Shumacker In the case of the larger shunts of true arteriovenous

fistulas, the proximal artery characteristically becomes dilated and tortuous with the passage of time

Simeone By virtue of factors, as yet unknown but to which the increased rate of blood flow may be related either as a cause or as an effect

Burton I do not believe we understand it at all This is one of the mysteries of hemodynamics There is a similar problem of "post-stenotic dilatation," and I defy anyone to explain why the artery dilates beyond the stenosis (which must lower the pressure) The factors which lead to chronic increase in size of vessels and to growth of new arteries, and so on, are completely mysterious *at the moment I cannot see any simple explanation for it*

Montgomery Is it too early to ask whether you think these dilated, large arteries are physiologic or pathologic? We know there is a wide physiologic range within which the main arteries can enlarge

Fremont Smith And if this is wholly inflammatory, if there is biphasal dilatation to this extent, would it be physiologic in response to the tissue damage, rather than pathologic?

Kulka I don t really have an answer These studies were preliminary experiments and we are only beginning to collect systematic data

Montgomery But didn t you say that it does occur central to the damaged tissue?

Kulka It does extend proximally, yes

Kark How far proximal?

Kulka We have not determined its proximal boundary

Burton What does the section of the wall of these dilated arteries look like? Does it show any reconstruction of the wall?

Kulka Figure 37 shows an artery from a 90 day lesion and there is a marked fibrous thickening of the intima It must have quite an effect on the contractile function of a vessel *to have* such a fibrous lining

Horvath But Figure 41 demonstrated the lumen of the artery and this implies that the lumen of this particular artery is reduced

Fremont Smith But it seems to me this is exactly the contrast This is a dilated artery in spite of the fact that its lumen would be reduced by the increased intimal tissue The lumen if it represents a dilated artery is larger

Kulka This is a cross section but the artery has collapsed post mortem The significance of the fibrous tissue is that it is not con tractile Once stretched, it would tend to remain dilated

Burton I think I can offer a possible explanation We have been working recently on the elastic constants of autopsy human arteries, and we have been trying to dissolve out specifically the elastin or the collagen When the elastin, which is mostly in the intima is destroyed by using an elastinase, the artery becomes considerably larger To me, this means that the elastic elements are tied to the collagen elements in such a way that the latter are pulled in When the elastic intima is destroyed, the wall becomes much larger We were astonished by this, but it is true in every case that we have done

A conceivable explanation would be that the cold injury had started a degeneration of the elastic intima (which is shown later on to be replaced by fibrous tissue) This, I would think from what we have seen, would increase the size of the artery

Kulka We have not done many elastic tissue stains as yet but in some older lesions there was definite destruction of internal elastic lamellae

Kark What did they show early?

Kulka With Verhoeff's elastic tissue stain we found no definite early changes We did not try the periodic acid Schiff technique

Fremont Smith It would be interesting to take out some arteries and measure their comparative elasticity or their volumetric give, both to longitudinal pull and to pumping fluid into them, because it seems as though at some stage at least that is what has happened

Kulka The arterial dilatation, as I said, was somewhat of a chance finding and, as yet, we do not know how best to fit it into the picture

I would now like to discuss briefly the muscle changes Necrosis of muscle was often patchy in distribution and occurred to a varying extent whenever the overlying skin had reached a temperature of −6°C Figure 42 shows skeletal muscle from the distal metatarsal region 3½ hours after the animal was removed from the freezer This particular animal was injected intra arterially with India ink but the capillaries were plugged by compacted red blood cells and little ink penetrated

Fuhrman How long after thawing did you inject the ink?

Kulka About 2½ hours afterward It took about one hour f the foot to thaw completely at room temperature after rem

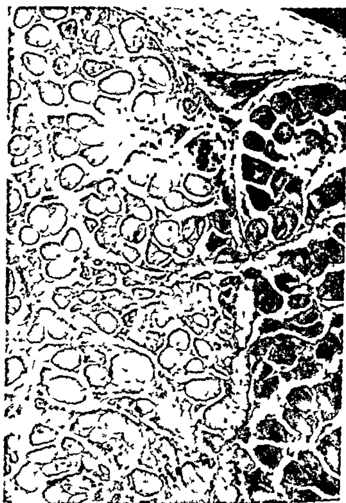


FIGURE 42 Skeletal muscle 3½ hours after moderately severe frostbite injury Some fibers show disintegration of the sarcoplasm (hematoxylin eosin stain x104) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

from the freezer Note the irregular disintegration of muscle fibers in some instances the axial sarcoplasm appears to be preferentially involved

In regions of more severe injury coagulation necrosis with increased eosinophilia of the sarcoplasm and loss of nuclei is found (Figure 43)

I might say that the muscle necrosis appeared to be followed by almost complete regeneration in about a year's time This sequence

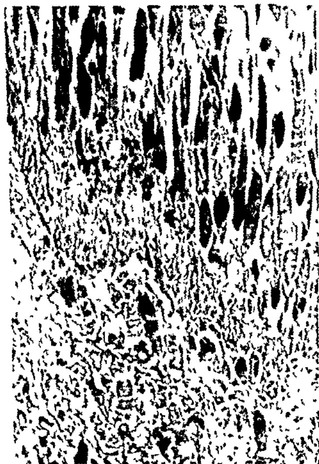


FIGURE 43 Skeletal muscle 8 days after severe frostbite injury The fibers above the fibrous septum were further distal and show coagulation necrosis The less severely injured proximal fibers below the septum show varying degrees of sarcoplasmic disintegration (hematoxylin eosin stain, x95) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

of events is in keeping with that reported following experimental ischemia in rabbit muscle (5)

Robert Lewis (6) has argued against ischemia as the mechanism by which such lesions are produced, since he found muscle changes as early as 15 minutes after a thirty minute exposure of a leg to a cold bath at −12°C This is much earlier than one would expect such changes to occur following ischemia alone In our experi

ments however, the possibility that ischemia contributed significantly to the development of muscle necrosis cannot be dismissed since a period of decreased circulation occurred before freezing as well as after thawing Muscle degeneration was still relatively slight 2½ hours after thawing

Montgomery Do you think the nuclei of the sarcolemma re-form in that muscle after necrosis of the muscle fibers itself?

Kulka It may depend on the intensity of the injury In the lytic type of muscle necrosis the interstitial tissue in the muscle and some of the sarcolemma nuclei seem to be preserved and so the regenerating muscle fibers grow back into their old sheaths In the coagulation type of necrosis which occurs with more severe degrees of injury I am not sure whether or not the sarcolemma is repaired or regenerated

Montgomery I wonder if they too re form after a year

Kulka We might now go on to discuss the bone changes The bone lesions are of particular interest because acute ischemia appears to be the cause of massive osteocytic necrosis Figure 44 illustrates a section from a metatarsal 8 hours after the animal was removed from the freezer There is extravasation of red blood cells focal capillary thrombosis and some leukocytic diapedesis into the Haversian canals The capillaries are not filled with compacted red blood cells as they are in most other tissues but nevertheless they were penetrated poorly if at all by intra arterially injected India ink

Some capillary flow must have existed after 4 hours since leukocytic immigration occurred between 4 and 8 hours after the animal was removed from the freezer

Note also that in Figure 44 the nuclei of the osteocytes show some vacuolation pyknosis and homogenization of the chromatin We are not certain whether or not those osteocytes were dead

It is interesting that the capillary changes like the arterial changes were segmental rather than uniform in distribution Similar segmental lesions were also apparent in the veins

Three days after freezing most osteocytes have become lysed and the periosteal cells are beginning to proliferate (Figure 45) This section came from the proximal portion of a metatarsal where injury was relatively mild and it is evident that some of the osteocytes immediately beneath the periosteum are preserved Since



Figure 44. Metatarsal bone 8 hours after frostbite. Extravasated red blood cells, focal capillary thrombosis and irregular staining of osteocyte nuclei are shown. Hematoxylin eosin stain × [illegible]. (Courtesy of the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D.C.)

the peripheral osteocytes presumably received the greatest cold exposure we are suggesting that they survived because they alone had access to an extra osseous blood supply.

Figure 46 shows bone 6 days after freezing. The osteocytes have disappeared from their lacunae. A layer of new bone is being formed by the periosteum and vascular resorption of the underlying dead bone has begun. Note the presence of an osteoclast.

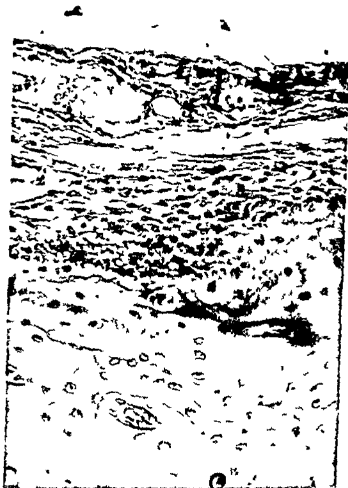


FIGURE 45 Metatarsal bone 3 days after frostbite There is lytic necrosis of all but a few subperiosteal osteocytes The overlying periosteum is hyperplastic (hematoxylin eosin stain x192) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

Kark Do you think that is a cyst?

Kulka No the resorptive process has not progressed that far

Kark Do you think this would account for what Dr Schatzki saw in the human subjects?

Kulka These resorptive and reparative changes may well account for some of the human roentgenologic findings but I have had no



FIGURE 46 Metatarsal bone 6 days after frostbite There is osteoid formation by the periosteum and beginning revascularization and resorption of the underlying dead cortex (hematoxylin eosin stain x252) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

personal experience with the bone pathology in human frostbite * Figure 47 shows bone 16 days after exposure Here the newly

*Through the courtesy of Dr Philip Le Compte Faulkner Hospital, Boston Mass we have since been able to examine histologically a frostbitten human foot with gangrenous toes which was amputated 21 days after exposure as well as the less severely injured toes of the other foot which were amputated 53 days after exposure The microscopic changes were comparable to those in the rabbit lesions including the selective necrosis of bone in parts which had not become gangrenous slow reconstruction of the dead osseous tissue with prominence of resorptive changes was apparent particularly at the articular margins



FIGURE 47 Metatarsal bone 16 days after frostbite There is a superficial zo of dense new periosteal bone New bone (see arrow) is being laid down with the widened revascularized canals (Hematoxylin eosin stain x166) Courtesy of th Armed Forces Institute of Pathology Walter Reed Army Medical Center Washngton D C

formed periosteal bone is already compact In addition a thin layer of new bone with a few osteocytes has been laid down within the widened revascularized Haversian canals There seems to be a real creeping substitution the dead bone acting as a template for reconstruction much like an autogenous bone graft It is evident that the deeper lying endosteal blood vessels have undergone necrosis This vascular necrosis occurs at about the same time as that of the bone

Figure 48 shows a mid-sagittal section of the terminal and middle p[illegible] a[illegible] a[illegible] character or thinner than its normal counterpart The normal thickness of the cortical bone is shown in the middle phalanx which is still about 90 per cent necrotic The reconstructive processes



FIGURE 49 Distal portion of toe 126 days after frostbite Conical shape and marked cortical resorption of the distal phalanx are shown The middle phalanx still has relatively normal proportions (hematoxylin-eosin stain x12) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

tend to proceed much more rapidly in the terminal phalanx than in the proximal phalanges The pointed shape and abnormally wide marrow cavity of the terminal phalanx are apparent Dr Schatzki has demonstrated these changes radiographically and they may persist one year after freezing

Bone necrosis occurs whenever there has been icing of the soft tissue It may extend into the metatarsals even when there is no permanent tissue loss Three dead phalanges and an almost dead metatarsal may form the skeletal support of a functioning digit.

Microscopic joint lesions were frequently present in the rabbits in the same location where Dr Schatzki found them in the human roentgenograms, that is, at the articular margins Figure 49 is a joint 2 days after exposure There is necrosis of the visceral synovial membrane and of the cartilage at the articular margin, as well as most of the bone In general, cartilage is relatively resistant to cold induced necrosis Some leukocytic infiltration is present in the necrotic tissues

Figure 50 illustrates an articular lesion 16 days after freezing Here fibrous tissue has filled the defect in the bone and cartilage at the joint margin and a thin fibrous pannus is growing over the remaining cartilage A deposit of fibrin-like material is shown within the synovial tissue This fibrin like material resembled that seen in rheumatic lesions and was also found in some joint lumens

Kulka Figure 51 is a joint lesion 333 days after exposure For several months before termination of the animal, this joint lacked full range of motion There is loss of cartilage over most of the joint surface with replacement by fibrous pannus

Lastly, I shall consider the massive necrosis of connective tissue which is associated with clinical gangrene This process differs from other types of freezing induced tissue damage in its delayed onset and is therefore most probably the result of some indirect mechanism Figure 52 shows an epidermal vesicle from a region which would in all likelihood have become gangrenous had the animal been allowed to survive Yet, the epidermis is far from being completely dead and is actually regenerating Moreover, no evidence of connective tissue necrosis is apparent India ink in jected intra arterially has failed to penetrate most of the superficial capillaries, but deep in the dermis some vessels are injected

Figure 53 represents a section through the proximal border of kin gangrene 4 days after freezing The zone of demarcation is ntensely infiltrated by neutrophils most of which are fragmented



FIGURE 49. Distal interphalangeal joint 44 hours after frostbite. Necro[illegible] an[illegible] neutrophil infiltration of the cartilage and endosteum at the articular margin ar[illegible] [illegible] (Hematoxylin-eosin stain, ×130). Courtesy of the Armed Forces Institute o[illegible] Pathology, Walter Reed Army Medical Center, Washington, D.C.

Proximal to this zone most vessels are permeated and surrounded by dense amorphous fibrin-like substance.

Figure 36 shows a longitudinal section of such a vessel under higher magnification. This animal was injected intra-arterially with a gelatin mass which does not penetrate capillaries. Since the mass fills the proximal portion of the vessel while the distal portion is obstructed by a thrombus, the vessel is probably an



FIGURE 50 Metatarsophalangeal joint 16 days after frostbite At the articular margin there is a defect filled by synovial connective tissue and fibrous pannus extends inward over the surface of the cartilage A deposit of fibrin like material is present in the superficial synovial tissue (hematoxylin eosin stain x100) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

artery The fibrin soaking and thrombosis of such vessels is a possible mechanism by which the gangrene might progress proximally

Hedblom Is that a typical thrombosis or is it the stasis that has been formerly mentioned in discussions by this group?

Kulka It is a typical thrombus composed of fibrin and presumably platelets



loss of
spaces
bone
stain
Army

Figure 54 on page 139 shows a region of early gangrene Most of the connective tissue is already dead and the only fixed cells with intact nuclei seem to be those in the walls of some large blood vessels Note the tremendous dilatation of these vessels Such vasoparalysis is rather characteristic of a gangrenous region

Crismon Were you able to make out any capillaries in that region or is it only blood in larger channels?

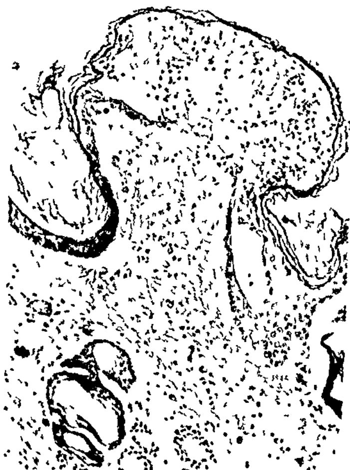


FIGURE 52 Epidermal vesicle 44 hours after severe frostbite Actively regenerating epidermis on the floor of the vesicle is shown Intra arterially injected India ink has failed to penetrate the superficial capillaries (hematoxylin eosin stain x159) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

Kulka The fresh blood is mainly in larger channels The capillaries tend to become filled with compacted red cells which obstruct further blood flow

Montgomery You could identify the packing of red cells in capillaries fairly early?

Kulka Yes By about 3½ hours after removal of the rabbit from the freezer most of the capillaries were filled with compacted red



FIGURE 53 Proximal border of skin gangrene 4 days after frostbite There is intense purulent infiltration at the zone of demarcation Most vessels proximal to this zone are permeated by a fibrin like substance (hematoxylin-eosin stain x41) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

cells and did not allow ink to penetrate In the larger vessels blood flow tended to persist until gangrene developed

Sweet Do I infer Dr Kulka you did not find it feasible to study the nerves by any technique?

Kulka We did not have the technical help to do special nerve stains However we could see in the hematoxylin eosin stained slides that there was definite nerve damage This damage was

manifested by occasional hemorrhages into nerve sheaths, myelin degeneration, and endoneural as well as perineural fibrosis

Kark Have you evaluated ground substance? Was there depolymerization?

Kulka No, we have not done much to study the ground substance During the proliferating stage, which begins about 3 days after freezing, there seems to be an increase in the interstitial ground substance, and the basophilic material in joints and tendon sheaths, but what happens to the ground substance initially, we have not attempted to evaluate

Hedblom An idea has crossed my mind during this discussion of pathology Can't an axiom be laid down that the degree of damage to various tissues is dependent almost directly on the degree of specialization of that tissue, ontologically speaking? The skin is the first one and it is the least affected, and then there are mesodermal tissues and the more highly specialized the mesodermal tissue, the more damage, there is the cartilage, which is affected early, at least before bone is affected, and then bone is next, and muscle next, bone is most greatly damaged

Kulka It is possible that tissue specialization may have some bearing on relative sensitivity to cold injury but from our observations it would appear that it is of greater importance in governing regenerative capacity and hence in determining the relative amount of permanent tissue damage For instance, the epidermis is not much more resistant to cold injury than bone, but regeneration of epidermis is rapid and the repair of bone is slow

I would like to re emphasize that it is difficult to generalize about tissue sensitivity to freezing cold, since the principal mechanism of damage may vary from one type of tissue to another For example we believe that the necrosis of bone follows reduction in intraosseous circulation The evidence for this etiology is first, within 8 hours after cold exposure India ink penetrates poorly if at all into bone capillaries second the capillaries tend to become compressed by extravasated red blood cells and white blood cells, third, thrombi develop fourth the peripheral osteocytes which have access to an extra-osseous blood supply are less uniformly damaged than deeper ones fifth, a somewhat similar type of bone necrosis occurs proximal to gangrene in a variety of human peripheral vascular disorders such as embolism and thrombosis (7)

The necrosis of arteriolar and arterial walls can hardly be attributed to ischemia since the walls of arterioles and at least the

inner layers of arteries receive their metabolic needs by diffusion from the lumens and blood flow as indicated by arteriography is not significantly impaired before the lesions develop If the lesions were a direct effect of freezing and thawing we would expect the arterial involvement to be more diffuse Thus the origin of the segmental vascular lesions, which appear within a few hours of cold exposure remains obscure

Finally it appears likely that the massive necrosis of connective tissue which takes place in gangrene is the result of indirect damage since it occurs after a delay of several days during which period tissue proliferation is evident The pathogenic mechanism of the gangrene may well be complex depending on the cumulative effect of several factors Since arterial thrombosis occurs proximal to the regions of gangrene it may well be important Other factors contributing to local ischemia may be the persisting capillary stasis and paralysis of arteriovenous anastomoses with short circuiting of the capillary beds

Permanent tissue loss is the resultant of direct injury from cold indirect effects such as ischemia and tissue regeneration

Shumacker With regard to these puzzling focal arterial lesions do you think there is a possibility that they may be caused by obstruction of the vasa vasorum?

Burton I was going to ask the same question because recently I was talking to Dr Durwood Smith of Vermont who has been working with radiation injury to blood vessels He finds the same focal character of its incidence His explanation was that the vasa vasorum are the most susceptible and it is because these little channels have been injured that this patchy focal injury occurs This would agree with your idea wouldn t it?

Shumacker I would think so Certainly there is some suggestive evidence that focal degenerative changes in arteries may be related to local changes in the vasa vasorum

Sellers Are there vasa vasorum in these arteries?

Kulka I know of no evidence that arteries smaller than 1 mm in diameter have vasa vasorum and even in larger arteries the inner portion of the media is nourished mainly by diffusion directly from the lumen Yet segmental lesions are present not only in the smallest arteries but even in arterioles and in larger arteries necrosis frequently involves the entire thickness of the media (Figure 34)

Shumacker I have the impression that Dr Winternitz s studies (8) led him to the conclusion that focal arteriosclerotic lesions

may be related to changes in the vasa vasorum even though th lesions are predominantly intimal and subintimal Has anyo really studied the problem and found out whether vasa vasora a actually present in these small vessels? They are certainly prese in veins

Kulka The German histologists have made comparative studie of the vasa vasorum and failed to find such vessels in arteries smaller than 1 mm in diameter (9) Winternitz demonstrated by India ink injection minute vessel like structures within the walls of larger arteries and arising from their lumens It is difficult however to interpret these apparent vasa vasorum since perfusion pressures of up to 1000 mm Hg were employed

Shumacker Dr Lowenberg and I (10) once did some studies using a technique that does not require injection of the vessel under high pressure This was the technique of O Neil (11) It essentially is a method in which the vasa are delineated by staining the erythrocytes within the vascular lumen with benzidine solution and then clearing the specimen The general anatomical pattern thus outlined was we thought quite similar to that which had been demonstrated by others with injection techniques

Kulka I still find it difficult to believe that arterial lesions of the type shown in Figure 55 on page 139 are the result of ischemia

Montgomery Was the blood flowing in that lumen?

Kulka Yes The red blood cells in the lumen are normal in appearance and in similarly prepared animals arteriography both *in vivo* and post mortem showed filling of such vessels

Crismon The intima looks considerably wrinkled

Kulka This is the constriction that takes place in normal arteries post mortem

Fremont Smith With regard to the bone changes hasn t it been reported in caisson disease that there are nitrogen bubbles that are emboli which lead to necroses in bone?

Kulka Yes

Fremont Smith Are they similar to this? That is without any inflammatory reaction It is a simple straightforward embolism a nitrogen bubble isn t it?

Kulka I have had no experience with caisson disease but there has been an experimental study of ischemia of bone induced by injecting charcoal (12) The lesions were not unlike those we find after freezing including the localized periosteal and endosteal new bone formation

It should also be added that Belloni (13 14) and Siegmund (quoted by Friedman) (15) who studied the histologic bone changes in human cold injury favored ischemia as the cause of the bone necrosis (13 15) and fat atrophy of the marrow (14)

Talbott Dr Kulka do you have any ideas as to the inability to reconcile your results with the studies of Colonel Lewis (16) in which the primary insult was in the muscle? Is it a difference of experimental technique? In each instance the same animals rabbits were used

Kulka The muscle changes we found 8 hours after freezing are not very different from those described by Colonel Lewis (16) but in contrast to his results after cold bath freezing we see only minimal muscle damage one half hour after exposure to cold air Therefore we are not yet in a position to say to what extent these changes are the result of a direct effect of cold and to what extent they are the result of ischemia

Blair In one phase our technique of producing injury may be a little different from Colonel Lewis's He produced cold injury involving the large thigh muscle of the rabbit where he only depilated the thigh and his damaged area was almost entirely muscle tissue His changes in muscle are appreciably different from those described by Dr Kulka but possibly the fact that that muscle was by far the overwhelmingly dominant material that he studied may have produced a greater influence on direct muscle damage as being the lesion of primary factor in cold injury

Our studies of course were made on the same animal but not with the same technique or in the same area or locale with the same large muscle masses I do not know whether that would possibly explain some of the difference or not

Crismon There was relatively little damage in the overlying skin in Colonel Lewis's demonstrations That was one striking thing and it is worth pointing out that the region is one relatively poor in arteriovenous anastomoses compared with the digit

Kulka Another thing that might be worth pointing out is that in the rabbit the skeletal muscle extends only to a point proximal to the metatarsal heads our animals did not receive the most severe cold exposure at this point The most severe cold exposure was distal to that

We also found necrosis of muscle beneath intact skin but only when the metatarsal skin temperature had dropped to −6°C and not much lower

Blair Deep tissue thermocouples going down to the bone itself would have been of value had we used them Bone has a very high conductivity for cold These peripheral bones where there is no insulation can conduct cold well back into the metatarsal area and may actually be colder than possibly the overlying skin which is highly vascularized We believe this to be true but have not proved it by using thermocouples

Montgomery Has anyone directly demonstrated by photography the penetration of a cell by the ice crystal?

Horvath Meryman did that a number of years ago (17)

Montgomery And it was successfully done?

Blair That is right

Montgomery Did that work demonstrate that ice crystals *per se* damage the tissues?

Behnke This was our opinion as a result of what appeared to be Dr Meryman s very conclusive work

With reference to bone injury isn t it true that one of the reasons that the bone is injured is that the vessels in passing through the bone cortex can be easily occluded because they cannot expand? In other words the condition is that of a vessel that can easily be in jured Dr Montgomery in your introduction you mentioned animal experiments in which the animals inhaled oxygen Would that have any bearing here on the supply of oxygen under these conditions?

Montgomery I cannot guess Our experiments are on prolonged chilling short of freezing and we studied the tension of oxygen in the tissue but with frozen tissue I should think our experiments have no necessary bearing

Behnke A lot of these changes are those that occur later

Montgomery After thawing I do not know if the tissue has a high oxygen tension or a low one up to the point at which the clogging of the capillaries occurs from the extruded serum I should think the oxygen tension would then be decreased if the tissues still use oxygen

Behnke These studies suggest a lot of therapy of various types but one type of therapy could be oxygen inhalation Did you carry the oxygen inhalation therapy beyond the period of cold exposure?

Montgomery In the first series we carried it through the 3 days of exposure We stopped then because that is about all a rabbit will stand without getting pulmonary lesions from prolonged high con centrations of oxygen In another group of rabbits we exposed the leg

to cold water and then administered oxygen by inhalation for the 3 days thereafter In these we could detect no benefit from the oxygen

Behnke You stated that oxygen was no more effective than the inhalation of air?

Montgomery The oxygen tension of the tissues increased to or above the preimmersion level when it was given during immersion in 3°C water In this series a slight but statistically significant advantage was gained in delaying the effect of the immersion foot Therapeutically it appeared to do a little good It did not prevent most of the damage but it certainly raised the oxygen tension markedly

Horvath The thing that worries me about much of this work on the freezing of tissues is that when we talk about cooling it down to such and such temperature we only talk about cooling the exterior down, but actually some of the interior tissues, for instance bone, may not be cooled to that extent A very nice measurement has been made of temperature in the medullary canal (18) For instance, at one point in the radius the temperature may be roughly around 20°C at various times whereas at another point it may be about 33°C, and there may also be that much difference in medial temperatures That may be exaggerated at the finger tips, so that when an area is cooled, there may actually be temperatures in these phalanges which are a number of degrees below that at the surface

Fremont Smith You mean the internal temperatures may be lower than the surface?

Horvath Correct Therefore, there may be an actual destructive effect upon the cell of the bone which is not evident from cursory examination This may explain some of the bone damage observed before we see it in other tissues

Fremont Smith How does the temperature get lower inside than outside?

Horvath It is conduction, outflow, many factors There have been several measurements of the gradients in the bone The temperature in the marrow of the bone can be quite a bit lower than that of the surrounding tissue

Burton All of it cannot be lower than surrounding temperature everywhere though at some points it can be lower, while some other places must be hotter than the surroundings

Fremont Smith Yes but it cannot be lower than any surface tissue You mean then, the surface immediately below I thought that was a mysterious statement

Horvath The gradient across is remarkably different Therefore, when it is cooled it may be at a much lower temperature so it may be possible to produce actual destruction of deep cells before it has begun to be produced at the surface

Montgomery By reason of conduction at the tip of the bone and by reason of the precooling of the arteriovenous back flow?

Fremont Smith I suppose, technically, the conjunction is heat rather than cold, it is the heat going out rather than the cold *coming in*

Horvath If a distinction between heat and cold can be made I will be very glad to have you do it

Fremont Smith I believe it was the absence of heat that gave you cold, wasn t it?

Andjus I would not expect such a difference in temperature between peripheral and deep tissues because *from the moment there is crystallization in the periphery, the latent heat of crystallization could prevent further cooling of the deeper tissues so that* in the bone and the marrow the temperature is held up at the freezing plateau ' even without the *occurrence of actual freezing* Do you have any evidence that there is some destruction in the bone produced by crystallization?

Kulka As yet we have made no temperature studies on the bone or any other studies that would tell us whether or not freezing of *the bone had occurred Since we were interested in studying the* chronic effects of cold as well as the acute, we have avoided perforating the skin to insert thermocouples because of the danger of infection at the point of insertion *

---

* Dr R A Wolbach in our l ... ere placed within the marr ... he soft tissue between meta ... the tip of toe 5 and overlying the thermocouple located in metatarsal 5 Following recovery from anesthesia the rabbit was exposed to air at −25°C The toe tip began to freeze while both the deep and superficial metatarsal temperatures were above 10°C ... tempera ... tissue ... skin ... vations ... rature ... both ... were in the midst of freezing ... ral but was again anesthetized ... amputated The skin dorsal to ... al 5 was frozen solid distally ... as only slushy These observa ... the overlying skin is unlikely

Andjus I think that if there is crystallization in the periphery, then deep temperature cannot go below the freezing plateau before the whole of the leg is crystallized

Blair You are correct, Dr Andjus, in that if freezing occurs there is a definite temperature plateau because of the heat of crystallization The point that I made previously, and that Dr Horvath also brought up, is not in contradiction to that at all We were suggesting that the cold transmitted along the shaft of the bone may cool that bone down considerably without any crystallization actually occurring in the foot Vasodilatation and spontaneous rewarming that occurs in soft tissues may not be so striking in bone I do not think bone ever rewarms to the degree that soft tissues overlying it do

Horvath So the total exposure of that bone to lower temperatures is markedly greater than the estimated exposure of, say, the surface?

Andjus But perhaps the temperature of the bone does not go as low perhaps it does not go below the freezing plateau

Blair That may be We cannot answer pro or con because the missing link in our experiments is the absence of thermocouples to measure bone temperatures The indication, from the pathology sections is that bone must get some cold injury that is not existent in the overlying soft tissues, and in an effort to explain this we have developed this theory as one of the possible mechanisms

Andjus Is it a secondary effect of ischemia or something of that nature?

Blair Possibly

Fuhrman There is another explanation, that one tissue is more sensitive to freezing than another We have been able to demonstrate that in vitro very nicely Skin is much more resistant than muscle

Blair Yes one criterion that Colonel Robert B Lewis (19) of the USAF School of Aviation Medicine stated was that tissues that are high in water content are apparently very susceptible to the direct effect of cold Skin is extremely low in water content and very resistant to cold injury, whereas muscle is extremely high in water content and very susceptible to cold injury

Fuhrman I do not think it is water content entirely

Blair No not altogether, but it is certainly a possibility I agree with you that it is not all water content Nerve is presumably very

susceptible to cold and its water content is not comparable to that of muscle

Horvath It may be related to the amount of free water and bound water Certainly the bound water is not going to crystallize, while the free water can

Fuhrman It may be related to the fat content, but I suspect it is more related to the type of enzyme system in the cell or the place in the cells where the enzymes are

Fremont-Smith I wonder whether or not on rethawing, it might not be found that in a complex enzyme system in which all parts are kept fairly well in balance, one or more of the enzymes are knocked out by the temperature and the others are not and, there fore, there is an imbalance and the release of enzymatic action which is ordinarily held in balance by inhibitors Such enzymes then might destroy particular tissue elements, if they are released Dr Burton spoke of enzymes that he used to destroy elastic layers within the blood vessels I wondered whether this kind of process could have taken place *in vivo*

Burton This is of course a rather foreign one We use an elastinase which is in crude trypsin I do not know whether there are such enzymes occurring in the blood or in vessel walls normally

Horvath It is true that a particular enzyme system may have a minor role at one temperature but at another temperature it may take over the major role and it may not be to the benefit of the organism for this system to have a major role in the metabolism of that tissue

Fremont Smith It may be held in check primarily by an in hibitor which may be susceptible to the temperature change and then released

Horvath I believe there is a large field of investigation possible in these temperature relationships of different enzyme systems and they certainly do not follow the same pattern We really know very little of what goes on in this particular area

Fuhrman Figure 56 shows the oxygen consumption rates of four different tissues after freezing for varying lengths of time They were small pieces of tissue, roughly about 100 mg, suspended in about 1 ml of Ringer's solution in an ordinary respirometer vessel Figure 57 shows anaerobic glycolysis

The oxygen consumption was determined on each sample at 37°C and then it was transferred to a bath at −25°C All of these

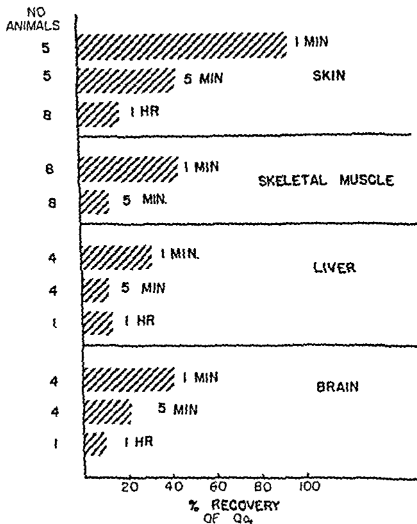


FIGURE 50. Per cent recovery of oxygen consumption after freezing. The four rat tissues were frozen in respirometer vessels for the times indicated. Initial and final rates of oxygen consumption were determined at 37.5 C

figures are for −25°C and the times given are from the moment of freezing in that −25 C bath. They usually supercooled. We have measurements with thermocouples in the vessels in other experiments. It is quite easy to tell when freezing occurs because

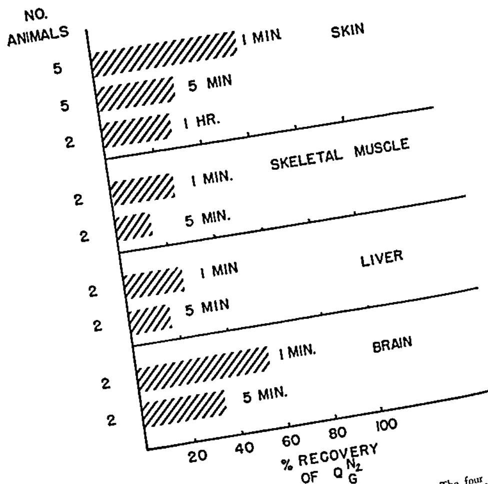


FIGURE 57 Per cent recovery of anaerobic glycolysis after freezing The four rat tissues were frozen in respirometer vessels for the times indicated Initial and final rates of anaerobic glycolysis were determined at 37 5°C

the whole material becomes opaque, so these short periods of freezing, the one-minute ones, are reasonably accurate

The tissues were then thawed by placing the vessels back at 37°C For one minute of freezing, the top bar in each group, the per cent recovery, given along the bottom, is highest for skin, lower in brain and skeletal muscle, and still lower in liver The brain and liver, of course, are only of academic interest so far as

frostbite goes but the reason they were run is that we know something more about their metabolism than we do about that of skin With a 5 minute exposure again the skin is more resistant

Figure 57 shows glycolysis done in the same way Again the skin is much more resistant to freezing than muscle

These experiments do not tell a great deal about the pattern of the effect of freezing on the enzyme systems because all there is to work with is the end measurement of a whole series of enzymes but it does appear that whatever is damaged is either one enzyme system common to both glycolysis and oxygen consumption or enzyme systems in general There has been one study on this by a group at Anchorage (20) who froze the mitochondrial system and measured the rates of the whole group of processes after freezing Unfortunately they did not time the freezing as far as I can tell from their paper Their preparations were frozen in dry ice at −79 C These systems did react differently to freezing under their conditions so that apparently some systems are damaged more by a given period of freezing than other systems

Sweet Each of the bars is the mean of the number of animals indicated on the ordinate?

Fuhrman Yes

Kulka Another chemical mechanism which might play a role in freezing injury is the local release of a histotoxic agent such as histamine as suggested by Lewis (21) Loos has reported that histamine like material is greatly increased in frostbite blisters (22) Such a toxic metabolite could exert a secondary injurious effect on the cells and their enzyme systems (23) Might it be possible that the enzymatic changes you have demonstrated are the result of such a secondary effect rather than of a primary effect of cold?

Horvath But the action of a drug is modified also by temperature because it depends upon the substrate the substrate available and the responsiveness of the substrate the enzyme system that it may or may not attack and things of that sort so I am not sure that these can be separated and called primary or secondary

Kulka Nevertheless this working hypothesis is appealing because it would explain why the tissue changes in such widely divergent types of injury as heat cold and hypersensitivity have so much in common

Fuhrman I think heat injury is something completely distinct from cold injury because denaturation of protein by heat can be shown This has not been clearly demonstrated with cold although

there is some suggestive evidence that something resembling it might occur

Kulka Wouldn't that depend on the degree of heat?

Fuhrman Yes, but so far as I remember from the data available (and I think Captain Behnke knows more about it than I do) irreversible changes begin from the heat at as low as 40°C if you extrapolate

Behnke Yes, there is a critical temperature, 44° or 45°C

Fuhrman And those changes, qualitatively, are indistinguishable from those produced by higher heat, isn't that right?

Behnke Yes, the changes are irreversible above 45°C

Crismon How good is the evidence for histamine release after cold injury?

Kulka The only direct evidence that I know of is the work done by Loos (22), who studied the histamine content of cold induced blisters and found it greatly increased

Horvath Increased over what?

Kulka Over normal blood

Fuhrman German groups have claimed increased histamine content of the blood and then used antihistaminics after frostbite and claimed they get less tissue loss

Hedblom Has anybody else done that?

Fuhrman Yes, there are at least two different groups who have used antihistaminics So far as I know, only one group claimed to show increased histamine content of the blood after frostbite, and that was Loos (24)

That the blood histamine level increased after frostbite was reported by Ziemke (25) Studies of the influence of antihistaminics on experimental frostbite have been reported by Frommel and Piquet (26), Macht, Bader, and Mead (27), Zetler (28,29), Dontenwill and Rotter (30), Dontenwill (31), Dontenwill and Zetler (32), and Meidinger and Kolsky (33)

Crismon There wasn't any detectable histamine in the edema fluid in our frostbitten rabbits, as I recall

Fuhrman Not as far as we were able to measure

Kulka The feature of frostbite lesions which is so difficult to explain on the basis of tissue susceptibility to cold is the focal distribution of some forms of tissue damage For instance, the epidermal necrosis is not diffuse, the bottoms of the hair follicles are much more resistant Yet in our preparations the entire skin was frozen solid

The milder lesions of skeletal muscle are also patchy but by far the best example of focal involvement is that of arteries I find these changes very difficult to explain on the basis of a direct effect of cold on tissue enzyme systems

Burton Doesn't this correspond to the physical picture, though? If there is supercooling, crystallization then begins It begins patchily, focally The forces which tend to cause ice crystals to form, operate some at one place and some at another Some of the factors are not known and some are known, such as surface tension differences, and the fact that there is a particle to start on Characteristically, the freezing of a liquid is a focal thing, and not general

Kulka I cannot visualize ice crystallization having the irregular distribution of the arterial lesions

Montgomery Dr Burton, you are speaking specifically about frostbite In immersion foot there is also a markedly focal reaction Wouldn't you say, Dr Kulka, since you have seen some of our preparations, that the damage is about as focal as that in frostbite?

Kulka They did tend to have a patchy character

Fuhrman Isn't it possible that those focal lesions are the result of ischemic changes?

Kulka Yes, except in the arteries

Montgomery If the focal damage is caused by vascular occlusion it must be from occlusion of very small vessels, perhaps arterioles or smaller, since the focal damage in the muscle is in such small areas Damaged areas may be only a fraction of a millimeter in diameter

Burton What is the scale of this patchiness?

Montgomery Sometimes only a few muscle fibers are involved in one high power field In immersion foot resulting from prolonged immersion most of the fibers are damaged

Burton What is the distance between this focus and the next one?

Kulka We are really talking about several different types of focal lesions The smallest are those in the arteries, and the blood vessels in general where a focal lesion might be no more than 100 μ in diameter (Figure 55)

Burton How big a gap to the next focus?

Kulka I cannot give you an exact answer but in Figure 55 the gap between two well defined foci is in the range of two to three times the diameter of a focus

Burton Is it a matter of thousands of cells or hundreds of cells?

Horvath Or is it only localized in that one spot?

Kulka In a single cross section of an artery, 8 hours after exposure it could involve a matter of 10 or 20 cells

Fremont Smith And there might not be any other foci visible in the whole field, isn't that right? It might be the only one in the whole field

Kulka That is true of well defined focal lesions but evidence of damage to scattered cells was usually present within the same high power field (Figure 55)

Horvath That is a cross section What about the longitudinal section along the artery?

Kulka The arteries in Figures 58 and 59 were sectioned more or less longitudinally

Horvath How far apart are they?

Kulka The focal lesions in Figure 58 are about 100 to 200 μ in diameter and the distances between them are about 400 to 600 μ

Horvath Did the two or three sections before or after this show any differentiation? What do you see on sections 10 μ in thickness?

Kulka I haven't seen enough serial sections to answer your question

Horvath You find this in a single isolated point Can we determine whether an artery is involved anywhere else? Is it just one local point? Is it just one area of damage and then no further injury in that same bone or that same muscle unit?

FIGURE 54 Region of gangrene 5 days after frostbite The nuclei in the walls of the engorged arteries tend to be relatively well preserved (hematoxylin eosin stain x63) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

FIGURE 55 Arteritis 8 hours after frostbite Focal intramural collection of neutrophils and scattered vacuolated medial cells are shown (hematoxylin eosin stain x135) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

FIGURE 58 Low power view of the artery depicted in Figure 34 Arrows point to foci of intramural hemorrhage and necrosis (hematoxylin eosin stain x55) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C

FIGURE 59 Segmental arteritis 6 days after frostbite The space occupying fibrin like infiltrate involves only part of the circumference of the vessel (hematoxylin eosin stain x90) Courtesy of the Armed Forces Institute of Pathology Walter Reed Army Medical Center Washington D C



F u r 51



F r 55



F r 58



F r 57

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Figure 56



Figure 5[illegible]



Figure 55

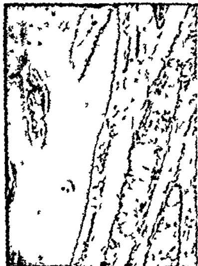


Figure 5[illegible]

Kulka In a low power microscopic field there might be two or three other arteries though perhaps not as big as the one in question and they might not show any lesions at all The skin and muscle lesions tend to be larger and less discrete than the vascular lesions

Horvath What about bone?

Kulka The lesions of bone are much more diffuse

Horvath Suppose that piece of limb that you froze was ½ inch in length how many of these focal masses would you see in that ½ inch of tissue? Or perhaps in another ½ inch on either side of the actual site or freezing? Would you see one isolated mass like this or would you find 10 or 500? I think the point is whether or not this may not be just an isolated phenomenon

Kulka In a ½ inch segment of the metatarsal region which has been briefly frozen all the compact bone dies In addition there will be some fat necrosis in both the marrow and the subcutaneous tissue Probably only one or two of the six or more major arteries will show focal lysis of the entire thickness of their walls In most of these arteries however there will be evidence of scattered damaged cells This minor damage is rapidly repaired by mitotic activity If the skin temperature had fallen below the freezing plateau to −6 C there would also be patchy necrosis of skeletal muscle With further cooling interfollicular necrosis of the skin appears and necrosis of the bone marrow is complete After a few days gangrene will involve this region if the animal has been exposed at −25 C for more than 40 minutes after the skin temperature has cooled below −6 C

Behnke There is no particular problem underlying the explanation of the skin focal lesion For example in ionizing radiation in the vicinity of the focal lesion there may be islands of epidermis around the hair follicles which will be intact and from which regeneration occurs The same is true following flash burns It is a matter of degree of penetration of the heat or of the ionizing radiation

Generally with reference to blood vessels aren't practically all lesions in a sense focal whether produced by spirochetes or various metabolic disturbances? In blood vessels there are areas of damage and areas in which the tissue is practically normal for example along a big vessel like the aorta

Kulka That is true but the basis for this curious distribution of vascular lesions has never been adequately explained

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Kulka The lesions of bone are much more diffuse

Horvath Suppose that piece of limb that you froze was ½ inch in length how many of these focal masses would you see in that ½ inch of tissue? Or perhaps in another ½ inch on either side of the actual site or freezing? Would you see one isolated mass like this or would you find 10 or 500? I think the point is whether or not this may not be just an isolated phenomenon

Kulka In a ½ inch segment of the metatarsal region which has been briefly frozen all the compact bone dies In addition there will be some fat necrosis in both the marrow and the subcutaneous tissue Probably only one or two of the six or more major arteries will show focal lysis of the entire thickness of their walls In most of these arteries however there will be evidence of scattered damaged cells This minor damage is rapidly repaired by mitotic activity If the skin temperature had fallen below the freezing plateau to −6°C there would also be patchy necrosis of skeletal muscle With further cooling interfollicular necrosis of the skin appears and necrosis of the bone marrow is complete After a few days gangrene will involve this region if the animal has been exposed at −25°C for more than 40 minutes after the skin temperature has cooled below −6 C

Behnke There is no particular problem underlying the explanation of the skin focal lesion For example in ionizing radiation in the vicinity of the focal lesion there may be islands of epidermis around the hair follicles which will be intact and from which regeneration occurs The same is true following flash burns It is a matter of degree of penetration of the heat or of the ionizing radiation

Generally with reference to blood vessels aren t practically all lesions in a sense focal whether produced by spirochetes or various metabolic disturbances? In blood vessels there are areas of damage and areas in which the tissue is practically normal for example along a big vessel like the aorta

Kulka That is true but the basis for this curious distribution of vascular lesions has never been adequately explained

Kulka In a low power microscopic field there might b t three other arteries though perh ps not as big as the one n | cs tion and they might not show ny lesions t all The sk n l m iscle lesions tend to be larger and less discrete th n the v sc l r lesions

Horvath What about bone?

Kulka The lesions of bone re much more diffuse

Horvath Suppose that piece of limb th t you froze was h in length how many of these focal masses would you s e tl it ½ inch of tissue? Or perhaps in nother ½ inch on either sid t tl actual site or freezing? Would you see one isolated mass l ke t or would you find 10 or 500? I think the point is whether this may not be just an isolated phenomenon

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Behnke Perhaps if we were working at a critical temperature at the time cooling was involved then the whole area would be involved It may be a matter of degree

Burton We would agree there was a population of thresholds of susceptibility of the different cells We might not agree on how wide the spread was You are working very close to the critical point where the ones which are most susceptible are just hit It might just be this factor might it not?

Kulka If only scattered single cells were damaged then it would be understandable in these terms but the fact that large patches of cells within an arterial wall are wiped out at one particular spot I find difficult to explain on the basis of a random variation in susceptibility of individual cells

Fuhrman Single cells could be susceptible and when the cell dies something may come out of it and spread around but it may not be histamine

Kulka Histamine is only one of many possible endogenous toxins whose release from an injured cell might initiate a local chain reaction

Horvath Which goes back to what I said namely that there is a different susceptibility of different cells and the fact that you may see 100 cells does not mean that all of the cells died at one time One of them may have gone the most susceptible one and in the next place where there is a patch or a gap there is again one cell gone

Burton The critical test of this hypothesis would be to give it more cold exposure Does the intensity of the lesion increase by having more patches closer together or does it increase by having the same number of patches but bigger areas? If the important factor is a population of susceptibility then in the colder temperatures when more exposure is given the patches should be closer together shouldn t they?

Montgomery In immersion foot certainly the longer that leg is cooled the more frequent the foci of damage and the more the total area of the damaged tissue is

Burton That is a rather critical test of the hypothesis

Kulka Unfortunately this test is difficult to apply in frostbite because with more severe degrees of cold exposure focal lesions are distinguishable only up to the time when gangrene develops

Burton When you say up to the time" do you mean actual duration of time or do you mean that with increasing cold expo

sure, the lesions remain focal until the point when there is immediate grangrene?

My suggestion is that the test of this hypothesis of susceptibility of cells being different would be to give longer exposure, or to lower the temperature, and then the cells that were not quite so susceptible would fail and, therefore, the foci should now be closer together

Fremont-Smith There should be more of the foci

Sellers Except, there are always other processes going on at the same time, for instance, like the formation of thrombi, and these produce their own chain of events which makes it difficult to be completely logical in approaching it as you are suggesting

Burton Very similar problems have been struggled with in radiation biology

Kulka Under mechanical stress, fluid and corpuscles will extravasate at some but not all junction points between endothelial cells as demonstrated in the Rumpel-Leede phenomenon I do have the impression that the blood vascular system is the shock organ in cold injury, it is where the most significant primary damage lies

Behnke Isn't it true that, with a certain degree of injury, for example, of the skin, the part may appear as though it were severely damaged and require amputation and yet under these conditions it has frequently occurred that there is complete regeneration of the skin from, say, the epithelial lining of the hair follicles? However, in a more severe degree of injury, there is no regeneration of the skin under the conditions in which connective tissue damage has occurred Perhaps, with reference to the skin it is a matter of degree of cooling and time of exposure

Kulka Some observations which may have a considerable bearing on this point were made by Dr Audrey Smith (31) She found that she could freeze an entire hamster solid without its getting frostbite if the animal's heart had stopped during preliminary body cooling Frostbite did occur in some animals if the heart was still beating at the time that the animal was frozen I would be very interested in hearing Dr Smith comment on this work

Smith I have a bit more to say about that presently, because I have done some more experiments since then If the heart is beating very strongly at the time the animal is immersed in the sub-zero bath, it is often possible to avoid that kind of frostbite that is if the animal has a really good peripheral circulation, or

Shumacker Captain Behnke, you began by saying that in some other injuries the epithelial tissue about hair follicles was preserved because it was less severely injured, is that correct?

Behnke Yes

Shumacker I think this matter has been demonstrated time and again in burns Would you not agree Dr Lewis? Often a burned area gives the appearance that all of the skin has been destroyed and yet in such cases there may be viable cells about hair follicles which quickly begin to grow spread and re epithelialize fairly large areas Correctly or incorrectly the concept has been held that being somewhat more remote from the surface these cells are less severely damaged This would have possible relationship only with focal lesions in the skin but I am inclined to believe that Captain Behnke is right

Kulka We must keep in mind that we are probably dealing with several distinct mechanisms of tissue injury The arterial lesions may differ in their pathogenesis from those in the skin and muscles but they highlight the problem of focal distribution

Burton I cannot quite understand your difficulty about the focal injuries It would seem to me much more astonishing in biology if you told me that all cells and all areas of blood vessel wall had the same threshold for injury That there is usually a wide population of thresholds is the factor we have to cope with in biology isn t that so? I would have expected that if the injury is just marginal which is your case here only the most susceptible cells are in question perhaps one here and the next there and the next there If you gave an intensity of exposure which was great enough I would expect the foci to come closer together

Kark Isn t it always like that? Consider a disease like membranous glomerulonephritis there is usually a membranous change that is generalized throughout the glomerular tuft but in diseases of reaction which people usually call the collagen diseases such as systemic lupus erythematosus there are local and focal changes (37) What is it that causes local changes in the glomeruli in systemic lupus erythematosus and what causes generalized changes such as are seen in membranous glomerulonephritis?

Horvath The factor may be different different susceptibility to a different set of stimuli

Fuhrman If red cells or bacteria are placed at low temperature death of all red cells or all bacteria does not result death of s

of them does, and if the time of exposure is increased or the temperature is lowered more of them die They do not all die at once

Fremont-Smith Or we see the effect of antibiotics on the cultures of bacteria I think it might be fair to say that there is room in what we know and can imagine around the situation, to find plenty of possibilities for focal lesions, focal evidences of injury, but that what we cannot do or come anywhere near doing at the moment is to specify at all what is the specific reason for a particular kind of focal injury, and I think that the general principle of populations of susceptibilities of either individual cells or groups of cells or organs or tissues is absolutely sound

This must operate, but what we cannot do and what we should do in this problem and in many others is to be able to specify exactly what happens in this particular case This, I think, takes us to an entirely new level of discourse of precision approach We do not know enough about what is occurring in most of these tissues in their growth and regeneration and development to particularize, and this is the problem we are talking about Isn't that what you are suggesting?

Kulka Yes I certainly appreciate Dr Burton's point of view with respect to random variation in cell susceptibility, but in addition it is necessary to postulate a chain reaction which kills the adjoining cells

Fremont-Smith Yes, unless the adjoining cells happen to be of the same susceptibility

Kulka But the distribution of these foci does not fit in with that of any known distribution of uniform cell populations

Burton At the risk of laboring the obvious, I think I can explain the two kinds of nephritis Imagine a population of thresholds of cells in the kidney which is like a gaussian error curve, in which the abscissa is the threshold intensity of stimulus" for injury, and the ordinate is the number of cells with this threshold susceptibility In one kind of nephritis the agent which causes it perhaps has an intensity so low that only a few of the cells will suffer from it The others will survive so there will result a patchy kind of lesion

But with another type of injurious agent there may be an intensity greater than the threshold of most of the cells, so that a complete lesion over the whole tissue may result

As you are probably working with a low intensity stimulus injuring with the frostbite only the most susceptible cells the crucial

test of this is that if you increase the intensity, then the scale of the mosaic of injury should get smaller.

Fremont-Smith: You are giving this an over-all explanation, but the pathologist, working with muscle, seeks for a specific mechanism. There might be twenty or fifty mechanisms which would all fit into this concept of individual injuries, isn't that fair to say?

Burton: This general idea has been so fruitful in, for example, respiration physiology, that it has been widely developed. Every alveolus has not the same ventilation.

Fremont-Smith: It gives the only answer in terms of that generalization and I think it applies very widely. What we are seeking for now is the particularization within the generalization.

Fuhrman: Dr. Kulka, do I understand that your objection to this sort of hypothesis is that you should get single cells dying instead of groups of cells?

Kulka: That is right.

Fuhrman: Couldn't it be that some local factors modify groups of cells, not single cells?

Burton: Or a single cell, if it is susceptible, triggers the population around it.

Kulka: We need to know what this triggering mechanism is.

Fuhrman: A certain group of cells may have an oxygen tension CO_2 tension different from another group of cells when the freezing takes place. That may modify the susceptibility, not of an individual cell but of this group of cells, so it need not be something released from a dead cell which triggers the cells around it.

Fremont-Smith: And it might be a younger cell field or older cells as Dr. Smith expressed it.

Behnke: I would suggest that cell susceptibility depends upon the stage of division. During a certain stage of cell division a cell may be susceptible or very resistant.

Kulka: I find it difficult to account for the distribution of arterial lesions shown in Figure 58 in terms of either oxygen tension or mitotic activity. To my knowledge there are no clumps of uniform cells with a distribution corresponding to that of the lesions.

Burton: But your view is not that those same cells were there a year ago, is it? Surely there is a turnover in the cells, even in the artery wall that is much faster than is generally thought. Some groups may be older than other groups of cells in the same wall.

Kulka I am not aware of any such focal cell turnover in arteries

Burton I know in the case of the endothelial cells this is true The individuals in the population are continually changing

Fremont Smith When new blood vessels grow new smooth muscle cells must grow also

Kulka But they do not grow in focal patches

Fremont Smith Probably not we do not know much about the growth of those blood vessels

Horvath The next section which you may take may show the distribution of those plaques of destruction to be slightly displaced from what they are now You may find another one is at a corner over at the next section

Kulka Right

Horvath So really it is impossible to say anything from this one figure as to the distribution of these patches all of them must be looked at It is the same old process again that a single cross sectional view tells nothing unless it is looked at in depth both vertical and horizontal

Fremont Smith It is interesting how much dissatisfaction we have here It is obvious that many tissues do have patchy lesions when they are injured It is also reasonable to think that there should be a susceptibility of injury I think that your dissatisfaction is Dr Kulka that you are seeking the mechanism for the particular and this is quite clearly beyond our level of knowledge at the present time All we can say is that there are various things that might enter in and they are probably none that we are thinking of there are probably some others at the higher finer levels of enzyme cancellations and so forth and this is the new era we must move into

Kulka I was hoping to stimulate someone into bringing new ideas to bear on such a mechanism

Kark There may be some studies that bear on it Wirz (38 39) in his studies looked at ice crystals in sections of kidney tissue while they were being warmed up from cold to quite warm temperatures He observed ice crystals melting at different temperatures because the crystals were bound with various amounts of electrolytes and their osmolar concentrations were different in different parts of the kidney Has anyone made any studies of the melting points of ice crystals in artery walls or other vessel walls?

Behnke We will hear about this later

Smith I have not done anything on the blood vessel wall

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CHANGES IN CELLULAR METABOLISM FOLLOWING EXPERIMENTAL COLD INJURY*

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THE WORK I SHOULD LIKE TO DESCRIBE was done in order to clarify the fundamental nature of the injury produced by freezing We were actually interested in some criterion of death of the cells some indication as to whether or not the cells were capable of recovery after freezing

We decided to use, as a measure of this, the rate of metabolism of the cells We have thus far been measuring oxygen consumption and glycolysis of the skin, as I mentioned earlier, and we are now extending this to other metabolic processes, but the material I will discuss is entirely concerned with those two types of metabolism

The first material I wish to mention was obtained after freezing skin *in vitro* We also have information about the metabolism of skin removed from injured feet of animals within a few hours or a few days after frostbite

This work was all done on rats because the skin from the dorsal surface of the rat's foot is an extremely satisfactory tissue for metabolic measurements When removed from rats weighing under 250 grams it is thin enough for adequate oxygen diffusion Also, it can be stripped off easily without very much damage We leave the adherent subcutaneous tissue on it and use a strip or a square of this skin which weighs somewhere between 50 and 100 mg, we measure the metabolism by the usual method On the other hand, the skin from the rabbit foot is too thick for adequate oxygen diffusion and it must be cut into slices which must produce considerable additional damage

We were first interested in attempting to quantitate the effects of freezing on metabolism of the skin There are, in the literature,

*This investigation was carried out in collaboration with Geraldine J Fuhrman and was supported by the Medical Research and Development Board Office of the Surgeon General Department of the Army under Contract No DA 49 007 MD 459

a number of isolated observations which indicate that freezing damages the metabolism of tissues Some of the better observations are those of Lynen (1 2) in Munich who showed that liver preparations after they were frozen had less oxygen uptake than when freshly prepared Similar observations were made in Argentina by de Robertis and Nowinski (3) and Kodama (4) made some other experiments At the first conference on cold injury Dr Crismon (5) reported some observations which Dr Field had *made on skin But few of these data had been obtained under* strictly quantitative conditions and it was very difficult to get any idea as to how much basic oxygen consumption or glycolysis or any other metabolic function remained in skin removed after frost bite because usually the skin was put in the deep freeze and then taken out and the metabolism was measured afterward

The method with skin was quite easy because the rate of metabolism of the skin from the dorsal surface of the rat s foot is constant for 4 or 5 hours if not longer at 37°C so we could use a single piece of skin measure its rate of metabolism initially at body temperature then freeze it for any desired period of time measure the rate of metabolism of the same piece of skin again and then express the second rate of metabolism as a per cent of the first for the same piece of tissue So we did not have to worry about whether to express this on a dry weight or wet weight basis

Table VIII shows some of these measurements on skin I do not have the numbers of samples but in general there are from 10 to 30 samples for each figure given The first one at 0 4°C was done to determine whether maintaining the tissue there for any very long time had any very marked effect on subsequent oxygen consumption and it was found that it did not The last column on the right indicates whether or not the tissue froze In this case of course it did not and the oxygen consumption was 105 per cent of the initial I suppose the experimental error is roughly of the order of plus or minus 5 or 7 per cent so essentially there is no change if the tissue is maintained at just below 0° for 24 hours If the tissue is placed in a bath at −5° or −6 5°C or −10°C and supercooled it seems to be purely random whether freezing occurs spontaneously or not at least down to −10 C so that it is quite easy to maintain the tissue in a bath at −6 5°C either frozen or unfrozen

One can produce freezing very easily after supercooling by giving the vessel a sharp tap and at −10°C some vessels freeze spontaneously and some do not Those which do not but supercool

TABLE VIII

Oxygen Consumption* of Rat Foot Skin After Cooling *In Vitro*

Temp (°C)	Time Cooled (hr)	Qo_2 (per cent)	Frozen
−0.4	22	105	No
−6.5	3	95	No
−10	1	83	Yes
−10	3	66	Yes
−10	3	131	No
−10	5	42	Yes
−10	18	8	Yes
−25	1	18	Yes
−25	3	11	Yes

*Qo_2 at 37.5°C after cooling is expressed as the percentage of the Qo_2 at 37.5°C before cooling

can be made to freeze by tapping the vessel. Table VIII also shows an exposure at −6.5°C for 3 hours without freezing. Again exposure for this period of time for that low temperature seems to have no effect on oxygen consumption. It may decrease it very slightly but probably not.

Then if freezing occurs, the third line at −10°C, the oxygen consumption is decreased to 83 per cent after freezing for an hour and to 66 per cent after freezing for 3 hours. In other words, at a given temperature, say −10°C, the longer the skin is frozen, the lower the oxygen consumption when it is brought back to 37°C.

The same thing is true of any other temperature. Here only the data at −25°C appear and the rate goes down to 18 per cent in one hour and 11 per cent at 3 hours. The damage to metabolism by freezing depends upon both the time of exposure to the given temperature and on the temperature to which the material is frozen.

The problem of supercooling is shown in Table IX, in which there are three temperatures used, −5°, −6.5°, and −10°C. The figures given are rates of oxygen consumption at 37.5°C after 3 hours exposure at the temperatures indicated, expressed as a percentages of the rates of oxygen consumption at 37.5°C before

TABLE IX

Oxygen Consumption* of Rat Foot Skin After Freezing or Supercooling *In Vitro*

Temperature to Which Cooled (°C)	Time Cooled (hr)	Number of Samples	Final Qo_2 as % of Initial	
−5°	3	16	98	Not frozen
−5°	3	11	77	Frozen
−6 5°	3	15	97	Not frozen
−6 5°	3	18	77	Frozen
−10°	3	12	131	Not frozen
−10°	3	18	66	Frozen

*The rate of oxygen consumption (Qo_2) was determined at 37 5°C the same samples were then cooled as indicated the Qo was then again determined at 37 5°C The final Qo is expressed as the per cent of the initial Qo

cooling The samples are separated into those which froze and those which supercooled without freezing It shows that if freezing occurs the lower the temperature the less the recovery

But the surprising thing is that, with supercooling without freezing at −5°C and −6 5°C, there is apparently no effect on oxygen consumption, but at −10°C there is a marked increase I have no idea what causes this and I would appreciate suggestions

At any rate, freezing does, then, inhibit oxygen consumption Glycolysis could be presented in much the same way. I have found that it is dependent upon both the time and the temperature of freezing

Since rapid warming, in my experiments, is a quite satisfactory means of preserving tissue after immersion frostbite, it was interesting to see whether rapid warming of tissue frozen *in vitro* had any effect This is shown in Table X in which there are two types of exposure Table X is per cent recovery of oxygen consumption and again, it is on the same piece of tissue There are six samples in each of these In the first line the tissue was frozen at −10°C for 3 hours and then half of the samples, six of the samples, were removed from the bath and permitted to thaw in room air These

TABLE X

Effect of Immediate Rapid Warming on Subsequent Oxygen Consumption* of Rat Foot Skin Frozen *In Vitro*

Temp (°C)	Freezing Time (hr)	No of samples	Thawing	Qo_2 as Per Cent of initial
−10	3	6	Air + 25°	45
−10	3	6	H_2O + 42°	68
−25	1	6	Air + 25°	18
−25	1	6	H_2O + 42°	26

*The initial rate of oxygen consumption (Qo_2) was determined at 37 5°C the samples were then frozen in the respirometer vessels as indicated Those to be thawed in air were removed from the thermostats left in air and carefully watched for signs of thawing At the moment thawing occurred duplicate samples were removed from the freezing bath and immersed in water at 42°C for one minute All samples were then re-oxygenated and the Qo_2 again determined at 37 5°C The second Qo_2 is expressed as a per cent of the initial Qo_2

were watched very carefully and when they had thawed the oth samples were taken out and immediately placed at 42°C for minute and then all were placed at 37°C and the oxygen consumption rate was measured The period of the frozen state then was identical in these two sets of experiments

With both of these types of freezing −10 C for 3 hours and −25 C for 1 hour the rate of oxygen consumption is higher in the rapidly warmed skin *in vitro* than it is in the skin thawed in air and these differences are statistically significant

The nature of the damage produced by freezing under these conditions and presumably in the intact animal has interested many of us I would like to discuss an explanation for this based largely upon Dr Lovelock's work (6) and Dr Smith's work and I hope that Dr Smith will interrupt me in the few things I want to say about it The idea is that the damage produced by freezing under these conditions may be caused by the high salt concentration produced by freezing out water as ice and it may not be caused by the presence of ice crystals as such the data I have are compatible with this point of view Dr Lovelock (6) using red cells found that hemolysis produced by freezing and thawing at various temperatures could be quantitatively reproduced by exposure of

the red cells to concentrated sodium chloride solutions and resuspension in normal saline without freezing I think he has carried the work further and has shown that there are changes in the membrane of the red cell at least in the lipoprotein fraction of the red cell with exposure to high salt concentrations and with freezing

Smith Dr Fuhrman it is the mucoproteins which dissolve in high salt concentrations at low temperatures and then are precipitated out (6) The lipoproteins and phospholipids are more involved in thermal shock (7)

Fuhrman Yes I was about to discuss that

Fremont Smith But the others were precipitated out and denatured is that it?

Smith Yes but this work has not yet been published in full A brief account can be found in the paper on thermal shock The protolipids break down and some of them are dissolved

Fremont Smith And denatured?

Smith Yes so the cells have lost a high proportion of the protolipids That is the main action of the strong salt concentrate formed during freezing The lipoproteins are also involved in the thermal shock part of it

Fuhrman I thought I recalled from a paper (8) that Lovelock published on work which he was doing on thermal shock in red cells that the same increase in cholesterol in the supernatant occurred with ordinary freezing as well as with thermal shock Am I correct?

Smith Yes there is a change in the cholesterol but less than in the phospholipids *

Fuhrman At least we can say there is a change in some protein component of the cell wall apparently both with thermal shock and with freezing The idea originated with Moran (9 10)

Smith Yes

Fuhrman Actually it originated with a botanist considerably before Moran (9 10) but the latter had evidence that this sort of thing occurred in eggs which were frozen

Smith And muscle It was not by any means original of course Breedis (11) and Moran (10) had thought of the same idea only they had not proved it quantitatively It was Lovelock who was able to prove it by precise physiochemical methods both for the

*Dr Lovelock says that Dr Fuhrman is right These facts were established between 1954 and 1955 while Dr Lovelock was working at Harvard Medical School He had lectured on this subject in the U S A without my knowledge

red blood cells and the spermatozoa He was able to predict, too, from the salt concentration which these cells would withstand at ordinary temperatures or temperatures just above zero, at what temperature they would be irreversibly destroyed, and how much glycerol would be needed to buffer the salt during freezing

Fuhrman This was such an attractive hypothesis to us that what we did was to test the effect of high salt concentration on the oxygen consumption and glycolysis of skin, because if the high salt concentration were the damaging factor, then there should be a decrease in the metabolism Apparently no one had done this before at least I had never found any information on it Salt concentrations not very different from isotonic had been used

Figure 60 shows the oxygen consumption and glycolysis The top curve is oxygen consumption denoted Q_{O_2} for skin, the middle one is glycolysis, and the lower one is simply the per cent water n the tissue after exposure for 1 hour and 15 minutes with salt oncentrations which range from approximately 0 15 molar on the r left to 1 6 molar on the right Salt concentrations of the order 0 8 molar, which was the concentration that was quite damaging to red cells severely inhibit both oxygen consumption and glycolysis

Smith In comparison with other living cells and tissues, red cells and skin are particularly resistant to freezing, and skin more so than red cells As much as 0 8 molar sodium chloride begins to cause damage to red blood cells, whereas here it shows quite clearly how much tougher the skin is and that there is really no very severe effect until a point between 0 8 and 1 2 molar has been reached

Fuhrman That is correct but there is also some inhibition at a much lower salt concentration so, presumably, if only a small amount of the water were converted to ice and the tissue maintained at that temperature for a long enough period of time, some damage would be expected This is not confined entirely to oxygen consumption but to glycolysis as well

Burton Are these rates of oxygen consumption measured while the tissue is bathed in the salt concentration or is this afterward?

Fuhrman These are measured while bathed in the salt solution, but if the tissue is washed and put in fresh Ringer's solution, about the same rate is obtained

Montgomery And these are at 38°C ?

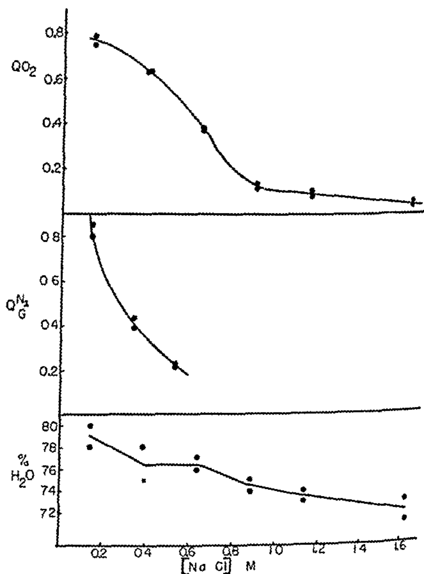


FIGURE 60 Effect of high salt concentration on metabolism and water content of rat foot skin *in vitro* The medium used was Ringer phosphate glucose to which more NaCl was added to give the desired concentration Qo and $Q_G^{N_2}$ were determined in the high salt media after about 1 hour in these media Water content was determined after the skin had been in the high salt media for 75 minutes

Fuhrman Yes At least these results are consistent with the idea that it is high salt concentration that is damaging the cells

Smith That is a very nice confirmation for Lovelock

Fuhrman The next problem was whether similar changes in metabolism occurred when the tissue was frozen *in situ* on the feet of the animal and here we were interested in testing whether the rate of metabolism immediately after thawing reached a low level and then stayed at that low level during several hours after thawing or whether there was further decrease in metabolism with time after thawing If the damage to metabolism is attributable entirely to the presence of the high salt concentration or to ice crystals or to something associated with freezing and thawing then there should be no decline in oxygen consumption or glycolysis as the time after thawing is increased

In the first place a number of control observations showed that here again the rate of oxygen consumption and glycolysis were dependent upon the duration of the frozen state and upon the temperature at which the frostbite was carried out There is no reason to go into it to give you the exact figures for that

At the last conference Dr Crismon presented some data of mine (12) which showed that the rate of oxygen consumption was increased in skin taken from frostbitten feet several days after injury I was not certain whether this was the result of some physiologic change or something else such as the presence of microorganisms since 3 or 4 days had elapsed after injury and the skin in common with other severely frostbitten tissues must have contained quite a few yeasts and other microorganisms

We attempted to ascertain which of these was correct by treating a group of animals with sulfonamide locally and with penicillin intramuscularly By this means measuring 2 days after injury we never obtained rates of oxygen consumption which were higher than 10 per cent of the initial control rate of oxygen consumption In other words the high figures which ran up to 200 or 300 per cent of the control were never obtained when efforts were made to prevent the presence of microorganisms Furthermore in one series of experiments fortuitously I suppose the skin from the untreated group of animals showed oxygen consumption rates which were identical with those from the animals which had the antibiotics Apparently in this one group the infection did not occur There appeared to be yeast like organisms in the scrapings from the skin of feet which had the unusually high rates of oxygen

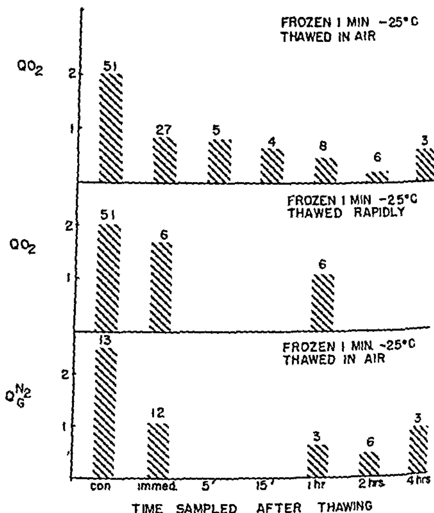


FIGURE 61 Metabolism of skin removed from frostbitten and control rat feet Qo_2 and $Q_G^{N_2}$ are expressed as microliters per milligram initial dry weight per hour Numbers above columns indicate number of animals used All feet were frozen by immersion at −25°C for the time necessary to freeze plus 1 minute Those rapidly thawed were then immersed in water at 42°C for 1 minute "Con" are determinations on skin from contralateral unfrozen feet, "immed" are determinations on skin taken immediately after thawing

consumption, so it may have been because of those, but we have not identified them

Because of these problems, we have confined our observations recently to the first few hours after injury where there is little likelihood that the rate of oxygen consumption can be influenced by the presence of bacteria or yeasts Figure 61 shows data which have been obtained on skin taken from frostbitten animals at various times after thawing All these were frostbitten by immersion at −25°C for 1 minute after freezing occurred The oxygen consumption is given in the upper graph and in this case the foot was thawed in air The rate of oxygen consumption, Q_{O_2}, plotted on the left, is expressed on a dry weight basis Wet weight would be unsatisfactory because the skin is edematous I will return to the middle graph later It shows the rapidly thawed animals, and the lower one shows glycolysis

In all cases the bar on the left is the control observation on the skin of the uninjured leg The second one marked "immed" is the oxygen consumption or glycolysis of skin taken immediately after thawing, just as soon as the skin softened to the point where it could be removed Then, subsequent bars show the rates of oxygen consumption or of glycolysis at different times 15 minutes, 1 hour 2 hours, and 4 hours The numbers on top of these bars give the number of animals used You will see that in the upper graph the oxygen consumption is very greatly decreased, as previously mentioned immediately after thawing from about 2 down to about 0 8 Then at later times after thawing there is a further decrease in oxygen consumption until it reaches its low point here at 2 hours after thawing.

I should not have made the 4 hour studies because the 2 day Q_{O_2} is just a little bit lower than the 2 hour Q_{O_2}, about 10 per cent of the control, and the series would have been very nice We ran three animals at 4 hours and obtained rates which were higher than at 2 hours I have no idea why It requires more animals to be certain if this rate is actually higher than at 2 hours *

At any rate, with glycolysis the same thing occurs the rate at 4 hours is higher than at 2 hours The rate of glycolysis is lower 2 hours after thawing than it is immediately after thawing In other words the damage produced by freezing is partly caused by something connected with freezing and thawing, or thawing

*Subsequent experiments show that both Q_{O_2} and $Q_{G}^{N_2}$ are slightly lower 4 hours after thawing than 2 hours after thawing

itself ice crystals or the high salt concentration which we think more likely But with time there appears to be further damage to the metabolism after thawing This appears to be ischemic damage or something associated with the circulatory change after thawing

The middle graph shows the effect of rapid thawing by immersion of the foot for one minute at 42°C If the middle graph is compared with the upper one at both time intervals shown immediately after thawing and 1 hour after thawing the oxygen consumption is considerably higher if the tissue is rapidly thawed than if it is permitted to thaw in air

One other observation which I would like to report very briefly and which is not related to this is as follows We have been interested in various means of modifying the extent of tissue loss following frostbite It was reported by Hoene (13) in Hans Selye's* laboratory that injuring a rat foot by heat reduced the severity of damage produced by a subsequent burn

In other words a mild burn tended to decrease the intensity of injury produced by a subsequent more severe burn We were interested in whether frostbite worked the same way and Table XI shows some figures on the amount of tissue loss using this method We dip one foot of an unanesthetized animal into a freezing mixture at −25 C for one second after freezing occurs This is not one second total exposure but we watch until the foot freezes wait one second and take it out Two days later we frostbite that same foot by immersion at −25°C for a constant period of exposure after freezing and compare the tissue loss in these animals with the tissue loss in feet of other animals which have not received the previous mild injury

The first set of observations simply shows that if the animals are pretreated the extent of loss is less than if the animals are not given this pretreatment I realize that this is completely contrary to experience in man

The time interval is critical in burns We have not studied it in frostbite but it is optimal at 2 days after injury in the case of burns

The second series of observations shows the same thing with different animals on a different diet and of a different size Originally we felt this was probably something related to the adrenal so we did this on a group of adrenalectomized animals the third

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TABLE XI

Modification of Frostbite by Previous Mild Cold Injury*

Pretreated	No of Animals	Frostbite −25° C (sec)	Foot loss (mm)
Yes	5	30	5 5
No	6	30	11 8
Yes	10	30	1 8
No	7	30	5 4
Adrenalectomized			
Yes	8	15	1 1
No	8	15	4 6
Sham adrenalectomized			
Yes	6	15	1 5
No	5	15	3 4

*The pretreatment consisted of immersion of one foot in liquid at −25°C for the time necessary to freeze plus one second The frostbite consisted of immersion at the same temperature for the time necessary to freeze plus that indicated in the table The interval between pretreatment and frostbite was 2 days

group of animals The initial mild injury decreased tissue loss after frostbite in these animals also At the bottom of the chart a group of sham adrenalectomized animals is shown

Conn Was the same foot immersed?

Fuhrman The same foot, yes

Conn What did you do with the other foot?

Fuhrman It does not show th[illegible] thing loo[illegible]

F[illegible]s some- [illegible] injury mize[illegible] the time been [illegible] before had they been adrenalecto- [illegible] of some duration?

Fuhrman Yes, it was 6 days These were all permitted to die without food, to make sure they were adrenalectomized If they did not die, they were not considered adrenalectomized

We tried to replace this mild injury We thought perhaps if this were stress we could replace the mild injury with cortisone but this did not have any effect on tissue loss

Travell What did you say was the optimum interval?

Fuhrman We did not determine it in frostbite but in burns it is 2 days After this the protection decreases with time and the relationship is a logarithmic one

Simeone What was this interval?

Fuhrman This is 2 days

Simeone What was the exposure of the tissue?

Fuhrman The initial exposure was freezing for one second at –25°C which produces a mild erythema and a slight edema that would be gone in one day I should say by the time this previously injured foot was frostbitten (2 days after it had been first injured) it would appear to be perfectly normal I suppose there could be changes in the bone but we do not have any histologic sections At any rate the volume is the same as it was initially The edema is completely gone and the amount of swelling after the second injury is the same in the control feet as in those with the previous injury

Horvath Does the more severe injury protect just as well?

Fuhrman I did not want to get into that because we produced just a little bit more severe injury and then there is edema present at the time the second injury is produced and this of course will modify that injury simply on the basis of size so the situation becomes rather complicated

Simeone You did not try possible protection in the contralateral foot?

Fuhrman Yes the contralateral foot reacts as a normal foot

Sellers How severe was the second injury?

Fuhrman Exposure at –25°C for 15 seconds 30 seconds or one minute after freezing The one minute exposure is enough to produce loss of all the digits in an untreated foot The 15 second exposure produces loss of tips of most of the toes only We have not tried the pretreatment with more severe injuries than the one minute exposure

Sellers But in each of those three degrees of second injury the same results are obtained?

Fuhrman Yes Initial mild injury reduces tissue loss in each case I should furthermore say that we also tried burning the foot

as the initial injury and then frostbiting it, and similar protection resulted It is a nonspecific thing of some sort

Conn How were the adrenalectomized animals maintained the 6 days prior to the initial exposure?

Fuhrman They were maintained on one per cent salt for the entire time They were actually maintained for 3 weeks, 6 days before the frostbite and 2 weeks thereafter

Kark *To go back to the first part of your work, I recall that* Lowry (14) has been studying various types of cellular respiration in tissues which are frozen and then immediately dehydrated When these tissues are restored to life by thawing to room temperatures and adding water, the respiration is not abnormal Could you or Dr Smith explain the difference between these findings and your findings?

Fuhrman He did not measure the respiration of the tissue but the activity of individual enzymes in it Is that correct?

Conn He has done both

Fuhrman I have never seen the other work in which he has measured the metabolism of the entire tissue

Horvath In those experiments, the salt concentration was up quite high since he dehydrates almost completely, and if this is at all a salt effect it should influence not only the oxygen consumption but also the activity of these enzyme systems

Fuhrman It is a matter of the salt concentration altering the cell membrane, so that what is left is a solution or suspension of *enzymes You never can reduce the oxygen consumption of these* frozen tissues to zero You can reduce it to about 10 per cent This probably behaves rather like an unfortified homogenate, so if that were fortified and concentrated in the right way, almost normal oxygen consumption might result

Horvath Or higher than normal

Fuhrman Perhaps higher than normal

Kark If the tissue is dehydrated, it expires in a manner of speaking

Fuhrman There is some respiration, yes

Behnke Dr Fuhrman in these tests in which the tissue was exposed to −10°C, under conditions of supercooling and ice crystal formation was there any difference subsequently in the respiration?

Fuhrman Yes, if the ice crystals formed the subsequent respira-

tion is damaged or decreased If ice crystals do not form at −10°C it is actually increased

Behnke With respect to rapid rewarming and warming in room air did you, in any experiments after warming in room air, bring the tissue up to 42°C and then down again?

Fuhrman No Actually, the tissue placed at 42°C never reaches 42°C We have measurements of that It reaches about 38°C with the duration of exposure that we use of one minute at plus 42°C so that the tissue is carried rapidly through a range of temperatures considerably below 42°C but it never reaches 42°C

Behnke At what temperature were the respiration experiments?

Fuhrman At 37 5°C Dr Montgomery told me that he has similar measurements of metabolism in immersion foot at various times after injury that I am interested in hearing about

Burton Why do you choose 37 5°C for skin temperatures? It seems to me a physiologist would avoid that No skin is ever at that temperature Why not use 34° or 33°C ?

Fuhrman Simply because of the convenience of comparing muscle with skin and we intend to use nerve It does not make much difference which temperature is chosen, it is mainly a matter of habit We have been accustomed to working on liver and brain and such things where 37°C is a reasonably good approximation If the optimum metabolism of the skin were at a temperature lower than 37°C there would be much better reason to use a lower temperature but it is not The optimum rate of metabolism as far as oxygen consumption goes appears to be around 40°C for the rat s skin

Fremont Smith This is optimum for oxygen consumption not optimum necessarily for the skin s happiness

Fuhrman Only oxygen consumption

Burton That makes it even less logical to use 37°C

Horvath It might explain the 130 to 131 per cent that you are getting which means that you are pushing these to optimum consumption

Fuhrman But those occurred after supercooling

Montgomery I am glad you used 37 5°C because I used 38 0°C and we can compare your results after freezing with ours after prolonged cooling short of freezing

Burton What is the use of having a whole lot of data that are comparable if they are not related to the physiology?

Conn What is the normal temperature of the liver?

Burton About 39°C

Horvath Yes 38° 39° or 40°C

Crismon In the period immediately after thawing the skin g up to temperature levels that are very close to deep body tempe ture for a short interval anyhow I think that there is some go reason for using those temperatures for skin on physiologic ground

Horvath But if it goes up to temperatures of near body temper ture which would be around 38° or 39°C or a little above 39°C then you are again measuring one at an optimum metabolism and another at far below optimum How can you compare the two?

Crismon You are studying the skin under temperature conditions that exist in the post injury stage

Horvath But not in the pre injury stage

Fremont Smith And very briefly

Crismon Ten minutes or so How long does the temperature stay up in the rabbit's foot? Is it a matter of 2 or 3 hours?

Fuhrman A few hours

Smith I think the most interesting result of all is the protection which you get in limbs previously exposed to injury Dr Fuhrman Is it something to do with the underlying circulation to the part?

Fuhrman I don't think it is caused by any circulatory change

Smith The first injury perhaps had increased the vascularity of the part or was it a biochemical change in the actual local tissues? I would like to know what you think about this whether it is a direct effect on the tissue or secondary effect

Fuhrman I rather think it is a direct effect on the tissue but I have no good evidence for that point of view The Canadian group thinks that it is caused by an alteration in the production of some substance that is assuming that the result of the second injury is caused by the liberation of something from the cell they think that the initial injury makes it more difficult for that material to get out of the cell blocks its exit from the cell or blocks its production or its effect

Smith It is odd that the optimum time was 2 days It seems as though if it had been a direct effect it might have been quicker something seen better within a few hours

Fuhrman I do not know what the optimum interval is in frost bitten animals

Fremont Smith Is the skin temperature modified after the 2 day period because this would be a measure of blood flow?

Fuhrman I have not measured it

Fremont Smith This might be a very simple way of checking that the vascularity had gone back to normal if the skin temperature was unchanged it would be very easy to do

Fuhrman There is no obvious hyperemia at that time the two feet look exactly the same

Simeone I realize there is some controversy on the subject but in some experiments we performed a couple of years ago on the freezing of sympathectomized tissue the sympathectomized ear of the rabbit to be specific the sympathectomy which did improve the circulation through the ear as measured by skin temperature did not protect the ear from the clinical effects of freezing So I would doubt that it was purely a circulatory problem

Fremont Smith That is a good point

Montgomery That was with very intense brine freezing?

Simeone Alcohol dry ice was used as the freezing bath

Montgomery Which might be quite different from borderline atmospheric temperature frostbite

Crismon It was the rabbit s ear?

Simeone This was the rabbit s ear

Crismon A difficult structure to save

Montgomery I think there is every reason to believe that the person who is thoroughly warm and thoroughly well fed is less subject to damage by a given exposure to cold This is especially true when as is usually the case the cold is not so intense as to threaten the tissues quickly

Behnke In line with the possibility of nonspecific reactions being protective I would like to call attention to the work of Killian (15) in Germany who found that the injection of a vaccine to produce hyperthermia in the treatment of frostbite was far more effective than hyperthermia induced by other means You might try something like a vaccine

Fuhrman I have tried it without success but it was given after the injury Did he give it before?

Behnke No he gave it afterward

Fremont Smith And then there is hyperthermia within an hour or two?

Fuhrman Yes As a matter of fact I did give it some experiments a few minutes before so that the hyperthermia followed

immediately, but it did not modify the injury at all That may only be because we have not arranged our dosage schedule properly

Smith Did you make any histologic studies on it? I think it is interesting, I would like to know whether you obtained a tremendous influx of leukocytes and macrophages and other cells into the part, and whether there was something of that kind

Fremont-Smith In the protected group?

Smith Yes

Fuhrman No, we have not

Fremont-Smith It would be interesting to do serially, if it were possible, in animals right up through a 4-day period at 6 hour intervals to see what waxed and waned histologically in that tissue during the protective phase, up to the maximum protection and down again

Smith I am sure Dr Kulka has some ideas about this

Kulka I would feel the same way you do

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EXPERIMENTAL IMMERSION FOOT IN THE RABBIT

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I WOULD LIKE TO POINT OUT first that the work we have been doing is on preparations that are somewhat different from any that have been formerly presented so far in the conference in that they are within the problem of experimental immersion foot This is not a problem of frostbite The animal we are using is the female rabbit *The leg is chilled for hours or days in flowing water at 3°C* Several of us have contributed to this work Dr Orville Horwitz, Miss Ann Sayen Mrs Charlotte Child Mr George Peirce, and, in the histological work Dr C G Tedeschi

It might be interesting to start by comparing our results in experimental immersion foot with the results of those of you who are making important observations in frostbite but I think it would be wiser to start with our methods and let the similarities and differences unfold

tory 2 days be

shows the ap

rabbit allows the left hindleg to be exposed to flowing water in a plexiglass chamber at 3°C and allows the right hindleg in another chamber to be protected from the water All four limbs can move freely and bear weight if the animal wishes but she cannot escape The rabbits eat well and eliminate urine and feces without contaminating the water or the box Four such devices can be run simultaneously if the water cooling is adequate The cold water is circulated from the tank which is shown in the background Cold exposures are usually made for times ranging from 4 to 120 hours The animals usually survive but an occasional one apparently weakened by an intercurrent disease dies during exposure

Figure 63 is presented primarily to show the relatively low and fluctuating temperatures of muscle and the very low subcutaneous temperatures All temperatures are taken with small copper con



FIGURE 62 Leg cooling apparatus

stantan thermocouples and are recorded every 2½ minutes by a Brown potentiometer. This figure spans the time between the 44th and 88th hours of exposure. Body temperature and the temperature of the muscle in the unexposed right leg are maintained at normal levels. The fluctuations of temperature of the chilled muscle are in response to fluctuations in blood flow occasioned by motion of the leg. Since this prolonged exposure to cold narcotizes the nerves of that part of the leg that is submerged, the muscles responsible for the motion are those above the level of the cold water. At point (*A*) the water was withdrawn from the leg and the temperature of the muscle rose to that of the control leg; there was little or no permanent damage to the circulation of the chilled leg after the 66 hours of exposure.

Figure 64 shows that there are considerable variations in the degree of chilling in one and another rabbit. This is true for both muscle and subcutaneous space. The water temperature was 3°C (±1°C) and the differences between tissue temperature and water temperature are plotted in order to eliminate the slight effect of this variation in water temperature. In the case of the temperature of muscle, some of the variations between different animals may be by reason of slightly different positions of the thermocouples in the

muscles but every attempt was made to minimize this Note that the fluctuations in temperature also vary from time to time and from animal to animal

Fremont Smith What does a block represent in this Figure 64?

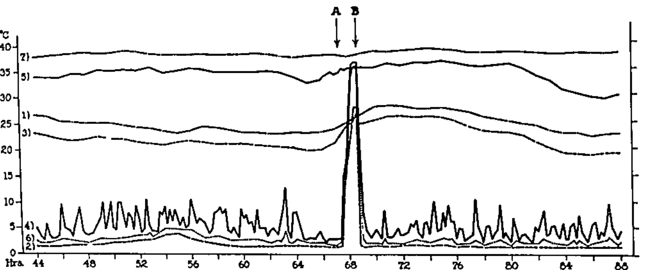
Montgomery It represents the temperature of the tissue above that of the water during the period of time given in the abscissa In the upper graph the tissue is anterior tibial muscle in the lower the overlying subcutaneous tissue

Fremont Smith What is the scale? Is that in degrees?

Montgomery The tallest block is about 8°C as is shown on the markings on the ordinate to the left The greatest fluctuations happened in this case also to be ±8°C It is important to note that the temperature varies from rabbit to rabbit and does not necessarily decrease with time A larger number of more recent experiments do show a tendency for the temperature of muscle to decrease with time especially in exposures of for more than 72 hours

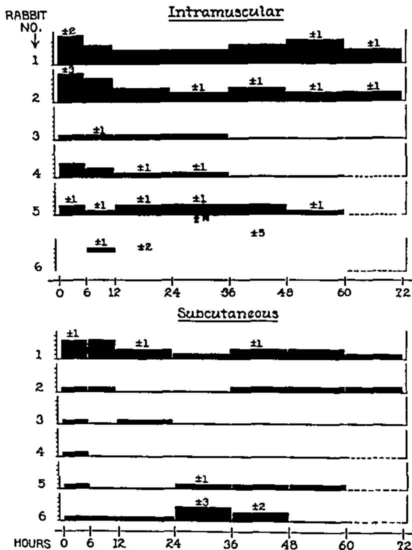
Several questions have been asked concerning the change in oxygen tension in chilled tissue Figure 65 shows the change in oxygen tension in rabbit muscle and subcutaneous tissue resulting from chilling by water at 3 C The superimposed effect of inhalation of pure oxygen is also shown For the measurement of changes in oxygen tension by the polarographic method small platinum electrodes were placed in the tissue and special precautions were taken to prevent any leak of current through the surrounding water As usual −0 6 volt was used The results are relative in that they were obtained from the measured changes in current but they have been corrected for the effect of changing temperature In general there is a tendency for the tension of oxygen in the tissues to decrease in response to the cold That is the decrease in circulation and the decrease in dissociation of oxygen from cold hemoglobin outrun the decrease in metabolism resulting from the cold This is not always the case as can be seen in this figure When the rabbit inhales oxygen the oxygen tension of the tissue increases The depression of oxygen tension by the exposure to cold is overcome by the effect of oxygen inhalation and in most instances the oxygen tension rises to values above those prior to exposure to cold

The inhalation of oxygen during the whole cold period did little to prevent the pathologic condition termed immersion foot In one series however that in which cold was applied for 30 hours there was a significant decrease in the neuromuscular dysfunction With longer periods of cold and of oxygen inhalation and with shorter



F GU E 63 Temp u s of water mu le ul utan ous p e b dy t ll nd r a und ontrol leg
1 = T C of the air surround ng the rabb t
2 T C of the water (or a r) su round ng the e posed (left) leg
3 = T C of the a r surround ng the unexposed (r gl t) leg
4 — T C of the mus le of tl e exposed (left) leg
5 — T C of the mus le of the unexpo ed (r ght) leg
6 — T C of the subcutaneous area of the exposed (left) leg
7 = T C of the body (subcutaneous belly aga nst dry wood)

At (A) the cold wa er was w thd a vn at (*B*) t was replaced Rep nted by perm ss on from Montgo nery H Horow tz O Pe ce G and Sayen A E pe men al mmers on foot I Tl e ffe s of p olonged exposure to water at 3 C on tl e oxygen tens on and t mperat e of the rabb t leg *J Cl n Invest gat on* 33 *361 (1 54)*



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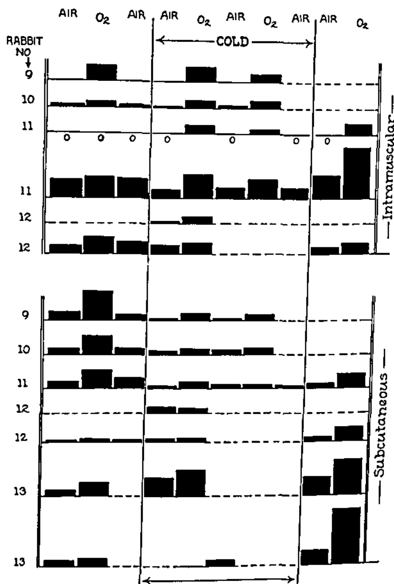


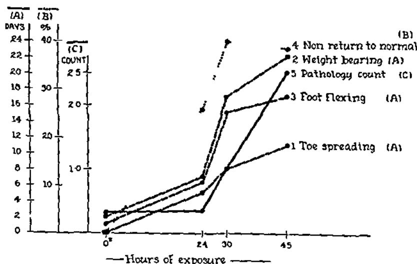
FIGURE 65 Effect of cold (3 ± 1°C water) exposure and of oxygen inhalation on the oxygen tension of leg muscle and of near by subcutaneous space The ... denotes air inhalation
2°C water
Reprinted
Sayen A
o water at
nvestigation

periods little or no advantage was gained We concluded that hypoxia is not the main cause of experimental immersion foot in the rabbit and by inference probably not the main cause in man

The inhalation of oxygen during cold increased the oxygen tension of the cold tissue to levels above those in the warm tissues On occasion there was little response but when working with these minute electrical currents measuring something like 10^8 amperes under water is difficult in fact this work has been more difficult than most of the rest of our oxygen tension work and probably not as accurate Nevertheless the over all results appear to be sound

Figure 66 shows that a number of changes take place to a striking degree after some 30 hours of chilling of the rabbit leg Certainly some begin before this and more severe changes take place later but those shown in this figure are not solely transient ones They are not measured during the exposure They represent the changes measured after the rewarming in room air All the following observations were also made following 2 or more hours after rewarming in this manner

Observations in Figure 66 were made 24 and more hours after completing the exposure with the exceptions referred to by the



asterisk The data are the means from studies of many rabbits, the details being given in the original paper (*A*) 1 is the average number of days necessary to regain ability to spread toes, 2 is the average number of days necessary to regain weight-bearing, and 3 is the average number of days necessary to regain ability to flex foot (*B*) 4 is the per cent of non-return to normal at end of 30 days (based only on toespread, foot flexing, and hopping) (*C*) 5 is the total pathologic "count" It concerns muscle only and is based on an empirical summation of degrees of fragmentation of fibers, edema giant cell formation, cellular infiltration, and basophilia 0° exposure is functional data for these points that were obtained from four rabbits subjected to apparatus for 50 hours without exposure of left leg to water at 3°C Pathologic 'count' for this point is that of a 30 hour exposure rabbits' average on right "unexposed' leg

Figure 67 introduces our more recent work on the effect of prolonged cold in water at 3°C upon the muscle and nerve of the leg

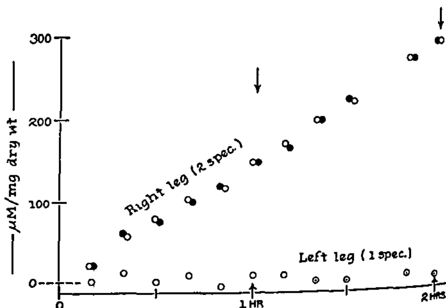


FIGURE 67 O_2 uptake by muscle of unexposed leg (right) and of 72 hours exposed (3°C water) leg (left) Specimens taken 2 hours after exposure and from Montgomery, H Experimental [m]uscle and nerve of the rabbit leg two [a]t 3°C *Tr Am Clin & Climatol A* [illegible]

of the rabbit * It is our first attempt to differentiate between the effect upon the function of muscle and the effect upon the function of nerve We chose to study the ability of each of these tissues to utilize oxygen 2 or more hours after a certain length of cold exposure The direct Warburg technique was used The modified phosphate buffer solution has been described elsewhere (1) This figure shows the rate of oxygen uptake by two specimens of control muscle (right leg) and by one of muscle in a leg (left leg) exposed to 3°C water for 72 hours and rewarmed at air temperature for 2 hours The Warburg is run at 38°C In this instance the muscle from the exposed leg was unable to utilize oxygen, the mean of six such experiments gave a low uptake of oxygen in the muscle

Fuhrman What muscle is this?

Montgomery This is the anterior tibial muscle

Fuhrman And sliced?

Montgomery The muscle bundles were cut lengthwise with fine scissors to a diameter of something under a millimeter We tried finer slices but this appeared to damage the tissue, since their utilization of oxygen was decreased We kept the tissue chilled from the time that it was taken from the leg until it was placed in the Warburg flasks at 38°C After reading your paper, Dr Fuhrman, on chilling during preparation (2) we were reassured concerning the chilling part of this technique

Figure 68 shows some mean values for oxygen uptake of muscle and of nerve from the same leg The black columns are of the left leg, the only leg exposed to the cold, and the open columns the tissues from the right (control) leg The posterior tibial nerve was used It is a slender nerve less than 1 mm in diameter, and is about 5 cm in length Slicing the nerve lengthwise did not improve its oxygen uptake, so it was used whole In the upper part of the figure the results are shown from four animals in which neither leg was exposed to cold Both legs in each of these serve as controls As in the others the uptakes of oxygen are given after ½, 1, and 2 hours

Below these are shown the results in animals having the left leg (black columns) exposed for 24 hours All animals shown in this figure and having a leg exposed to cold were sacrificed 2 to 3 hours after termination of the exposure The ability for muscle to utilize oxygen decreases with the duration of previous exposures the nerve is much less affected

*This work was supported by a research contract between the University of Pennsylvania and the Office of Naval Research

The next series of columns shows the change in weight of the whole muscle (anterior tibial) from which the specimens were taken At 1 and 2 months after exposure the weight of the muscle of the previously exposed leg decreases to about half the weight of the control by 6 months after the exposure it has returned to near normal

At the bottom of the figure is shown the summarized histologic data which to a degree correlate with the data shown above After Dr Tedeschi our pathologist had examined slides of all the muscles from which we had taken Warburg specimens and before he knew the results of the Warburg studies I asked him to tell me which in his opinion had low and which had high uptakes of oxygen From these slides he foretold the oxygen uptakes with an accuracy which to me not a pathologist was very remarkable

Encouraged by this I have placed what he summarized from a study of the histologic slides at the bottom of this figure He spoke of a marked degenerative phase immediately after and perhaps during the exposure to cold but also pointed out that even in the slides made from muscle taken 3 hours after the 72 hours of exposure there is already a beginning phase of regeneration This phase is most active a little later and is not wholly complete 6 months later In rabbits the most marked histologic evidences of inflammation were apparent within a few hours or days after the termination of exposure and we might have found this exudative response earlier had we obtained histologic material during the process of cooling The inflammatory response had decreased somewhat by the end of the first week and apparently had subsided by the end of the first month Judging from this and from the clinical (human) exudative phase described by Ungley and Blackwood (3) the exudative (inflammatory) stage in man may be more prolonged than that in the rabbit Our notes on the appearance of the rabbit leg at various times after exposure are not sufficiently detailed to afford a "clinical" comparison of our findings in the rabbit with those of Ungley and Blackwood (3) in man Furthermore simple visual observation and measurements of surface temperatures would apply to changes in skin the skin of the rabbit is so different from that of man that we think it unwise to make comparisons

With that much introduction I should like to show some photographs that illustrate the histology These were taken at different

times after the 72 hour exposure period Figure 70 reminds us what normal rabbit muscle looks like and it looks much like human muscle In looking at the subsequent photographs of muscle damaged by cold those of us who are not anatomists or pathologists should remember that the normal muscle fiber in cross section looks polygonal the sarcolemmal nuclei are arranged eccentrically there are no extracellular collections of fluid fibrin leukocytes fibroblasts or mast cells blood vessels including capillaries have a regular and mature look and connective tissue is minimal except as it surrounds blood vessels

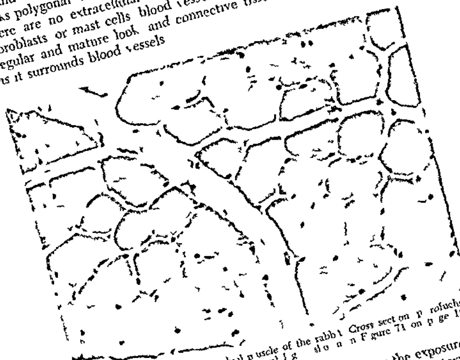


Figure 70 Normal anterior tibial muscle of the rabbit Cross section picrofuchsin stain x275 Muscle from the contralateral leg shown in Figure 71 on page 186

Figure 71 shows muscle 3 hours after completing the exposure to cold The tinctorial properties are altered basophilic in hematoxylin eosin staining There are deposits of fibrin in enlarged spaces between the muscle fibers and bundles The fibers are swollen and have lost their angular appearance and vacuolization is beginning Some of the sarcolemmal nuclei have wandered into the muscle fibers A few of these nuclei are swollen and this may represent an early attempt at proliferation All of the slides were stained with Van Giesen's picrotoxin stain so this normal appearing connective

FIGURE 71 Anterior tibial muscle 3 hours after exposure of this leg for 72 hours to water at 3°C Cross section, picrofuchsin stain, x275 Muscle from the contra lateral (control) leg is shown in Figure 70 on page 185

...RE 72 Anterior tibial muscle 1 day after exposure of the leg for 72 h... ...ater at 3°C Cross section picrofuchsin... ...es inflammation and ed...

tissue around the blood vessels and nerves shows clearly Small arteries, veins, and capillaries are engorged, but no new vascularization is apparent

Figure 72 is an illustration of a specimen taken one day after the exposure was completed In the exposed leg there was still drop foot and complete inability to spread the toes There is marked vacuolization of many muscle fibers, as evidence of breakdown of sarcoplasm Most of the nuclei have wandered centrally, or are grouped in rows somewhat away from the sarcolemma, and some of the nuclei are enlarged The nuclear changes suggest beginning regeneration of muscle fibers The enlarged spaces between the fibers and between the bundles of fibers contain fibrin and a few polymorphonuclear leukocytes and erythrocytes

These evidences of damage are focal in nature and some microscopic fields nearby show only minimal changes this focal nature of the lesion is characteristic of the specimens obtained at each of the times following exposure

Figure 73 shows a somewhat oblique section from muscle taken 3 days after the usual exposure Loss of sarcoplasm across whole fibers makes vacuolization less apparent Edema fibrin deposits and extravasation persist though perhaps to a less extent The centrally placed nuclei are of various sizes some greatly enlarged and are intermixed with macrophages There is abundant cellular infiltration between the muscle fibers some being polymorphonuclear leukocytes some mesenchymal cells and some perhaps sarcolemmal nuclei

Figure 74 shows part of a large damaged focus one week after completion of the usual exposure to cold Perhaps such foci in immersion foot are larger than those shown by Dr Kulka in response to actual freezing Though we have tried to choose these pictures as representative of the sequence of changes that take place with the passage of time after exposure, the focal nature of the lesions makes this difficult In this figure it is difficult to identify with certainty any single muscle fiber I suppose many of these cells are regenerating muscle fiber Dr Kulka when I showed him this was not sure whether the larger cells are original muscle fibers invaded by macrophages or whether they too are fibers regenerating from sarcolemmal masses nor was Dr Tedeschi sure

Nevertheless I think we would all agree that most of the mass of cells in this figure are muscle fibers in some state of regeneration

FIGURE 73 Anterior tibial muscle 3 days after exposure of this leg for 7 hours to water at 3 C Oblique section picrofuchsin stain x?75 Further evidences of regeneration

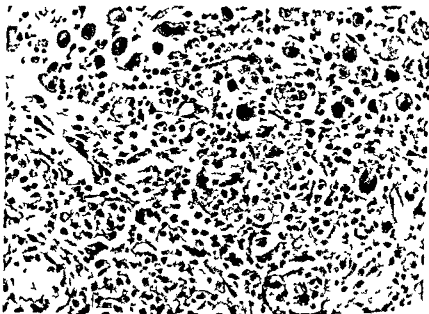


FIGURE 74 Anterior tibial muscle 1 week after exposure of this leg for ?7 hours to water at 3 C Cross section picrofuchsin stain x?75 Extensive regressive changes pronounced signs of regeneration

etween them there are distinct evidences of fibroblastic prolifera on though fibroblasts and histiocytes are not readily distinguished n some areas Dr Tedeschi recognized an occasional macrophage Regenerating capillaries are in evidence also The process is pri marily one of regeneration in a severely damaged area and though fibrin seems to have disappeared there is still some inflammation some leukocytic infiltration

Figure 75 shows the characteristic appearance one month after exposure Some of the muscle fibers look nearly normal in size and shape, some show vigorous regeneration and a few still seem to need repair Edema and fibrinous exudate between fibers and fas cicles have disappeared and extravasated polymorphonuclear leuk ocytes and red cells are not in evidence the evidences of inflamma tion have decreased The spaces between individual fibers have disappeared and the endomysium resembles that of the control except that there is an increase in connective tissue A similar in crease in connective tissue is seen between the muscle bundles The general appearance at one month is one of improvement The gross function of the rabbit s leg is improved but three of the six animals still were unable to spread their toes

I am not a pathologist I wish one of you would comment on our interpretation of the slides up to this point or on anything I have omitted

Kulka I think that these changes are qualitatively quite similar to those in freezing injury of rabbit feet There is necrosis of muscle and subsequent regeneration

Montgomery Am I wrong in trying to relate the sequence in oxygen uptake to the histologic sequence? The two sets of observations were made separately originally and I am trying to bring them together here for the first time

Kulka Your chemical findings appear to fit very well with the histologic changes

Montgomery Figure 76 is a photograph of the anterior tibial muscle and the posterior tibial nerve of the exposed and control legs These specimens were removed after sacrificing the animal one month after completing 72 hours of cold exposure Whereas the control muscle weighs 1 1000 of the weight of the rabbit the muscle from the previously chilled leg weighs 1 2000

Fuhrman Is that nerve actually larger on the right than the left?

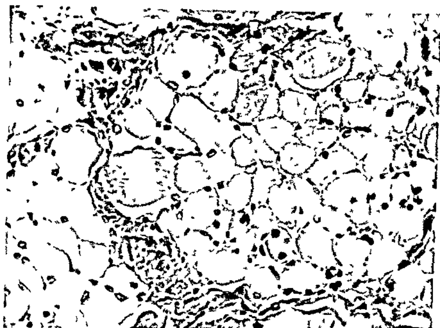
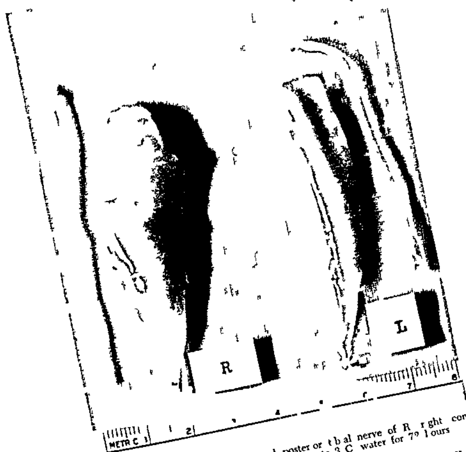


FIGURE 75 Anterior tibial muscle 1 month after exposure of this leg for 72 hours to water at 3°C Cross section picrofuchsin stain ×275 Extensive regeneration residual damage and atrophy and collagen deposit

Montgomery The nerve of the exposed leg is thicker than that of the control, and this seemed generally to be the case We did not weigh the whole nerves because it did not seem feasible to excise whole nerves or identical portions of nerves Some information on this may come later from analyzing our data on dry-wet ratios and on rough estimates of the fat in the many specimens In general the nerves of both legs get fatter with age, but I have the impression that this is especially true of the nerves that had been exposed to cold

Figure 77 shows changes 2 months after enduring the usual exposure to cold The changes are not very different from those after one month, except for marked fibrous thickening of at least the adventitia of a middle sized artery and replacement of some muscle fibers by fat cells This figure shows extensive areas of excessive connective tissue There are still some centrally placed nuclei presumably representing regeneration The total muscle is still atrophied as shown by the fact that it weighs only half as much as the



GURE 6 Anterior t b al muscle and poster or t b al nerve of R r ght control eg and L l ft leg e po ed 1 nontl p e ously to 3 C water for 72 l ours

control specimen Inflammatory elements are lacking Capillaries appear mature There was no gross functional disorder of the legs of the six rabbits studied 2 or 6 months after exposure no inability to spread the toes and no drop foot The adventitia of the large vessels is abnormal is it not Dr Kulka?

Kulka I could not be sure There appears to be a little fibrosis at the margin of the field where there are small muscle fibers with central nuclei

rewarmed to normal temperature, I have measured the oxygen consumption rate during the first 3 to 5 days after rewarming. The oxygen consumption was measured at two different ambient temperatures: at 30° to 32°C, where we measure the basal metabolic rate, and at a lower ambient temperature of about 20°C.

During the first 24 hours after rewarming, the oxygen consumption is somewhat lower than normal. The basal metabolic rate is lower than normal, and the chemical thermoregulation is absent. That is to say that the oxygen consumption is much the same at 30° and at 20°C.

Fremont-Smith: Are those degrees of animal temperature or environmental temperature?

Andjus: Environmental temperatures. Animals are rewarmed and oxygen consumption is measured at normal body temperature. During the first day after reanimation the oxygen consumption is lower at 30°C than that corresponding to the basal metabolic rate. At 20°C, however, there is no increase in the oxygen consumption; chemical heat regulation is completely absent.

Fremont-Smith: In other words, body temperature would fall?

Andjus: That is right. But the next day there is some chemical heat regulation in the reanimated animal, that is, a difference between the basal metabolic rate and the oxygen consumption measured at 20°C, but heat production is still not sufficiently increased to keep the animal's temperature at normal level. After the third day, however, the basal metabolic rate is usually normal, and at 20°C the increase in oxygen consumption rate is more adequate.

Someone: Did the respiratory quotient change?

Andjus: Yes, it did. The first hours after rewarming the respiratory quotient is about 1; then it comes back to normal.

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A PRELIMINARY FOLLOW UP REPORT ON CASES OF COLD INJURY FROM WORLD WAR II

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SHORTLY AFTER THE END OF WORLD WAR II it became apparent that the Armed Services would possess an unprecedented store of information pertaining to both disease and injury in a large population Records were on hand and could be made available for follow up studies of a number of conditions Through a co operative effort therefore of the Veterans Administration and the National Research Council a Committee on Veterans Medical Problems was set up which would consider plans for performing certain follow up studies Among the conditions to be so studied was Cold Injury in veterans of World War II It was foreseen that statistical considerations would be a major part of such follow up studies and the National Research Council assumed the responsibility for statistical evaluation and for abstraction and reproduction of medical records

The follow up study of veterans of World War II who had incurred cold injury was undertaken with the following objectives (1) to learn the physical status of veterans who had incurred this injury and to see if that status could be related to characteristics of the initial injury and to its treatment (2) to discover whether or not there might be any objective physical findings and laboratory tests which would be characteristic of cold injury and which might be correlated in degree with the severity of the injury and the subjective complaints and (3) to determine if personal or other factors in addition to the severity and treatment of the injury would influence the veteran s present physical social and economic status Furthermore it was expected that additional data would be obtained from the anamnesis to substantiate or expand the present concepts regarding the prevention and management of this condition

At the outset it was thought desirable to study a sample of veterans with nation-wide representation For this reason vascular laboratories were selected for this project in widely separated centers, namely, Atlanta, Chicago, Cleveland, New Haven and New Orleans

This kind of study has its advantages and disadvantages It has the advantage over the study upon which Colonel Blair reported in that a greater number of cases can be studied, a greater number of investigators can contribute to the study, and nation wide representation can be achieved with regard to sample On the other hand, it lacks the uniformity of a study such as Colonel Blair's in which he himself examined the fifty soldiers or veterans, interpreted their answers to questions, evaluated their subjective complaints and recorded the relevant physical findings all in the same manner Undoubtedly, Colonel Blair would record the degree of pallor of the toes with evaluation of the leg in the same manner for all cases In our study, it would be unlikely that similar uniformity would exist in five separate centers even though experts in the field were in charge Lack of uniformity would be greatest where the possibility for subjective judgment was greatest In the preliminary evaluation of the data, variation among centers has in fact been apparent, but how much of a problem this will present remains to be seen In the case of laboratory data, variations in the details of performing the tests have undoubtedly contributed to some lack of uniformity among the centers

The data obtained at each of the centers were recorded in code books for each of the veterans and submitted to Gilbert W Beebe* who with his staff assembled the data and subjected them to careful statistical analysis The interpretation of the data is not yet complete but some brief comments may be made regarding information obtained from the laboratory examination of this group of veterans These data are not all my own †

The veterans studied had cold injury of the lower extremities In most instances both right and left sides were affected It was found that the two lower extremities were so nearly identical in degree

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Problems
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School o ... William W L Glenn and his
assistants ... Haven Connecticut Dr F A
Simeone ... University School of Medicine
Cleveland Ohio

of involvement that for statistical purposes we may speak of limbs rather than of persons and the data are handled accordingly. Much of the data was obtained from 1061 limbs. Of these 461 were described as mild, 444 moderately severe, and 156 severe injuries. These numbers are not indicative of the normal occurrence in an injured population but were specifically selected to permit the study of adequate samples in each category.

The classification into mild, moderately severe, and severe cases primarily depended upon the presence or absence of blisters, superficial necrosis, and deep necrosis. By deep necrosis was meant gangrene extending beyond the thickness of the skin. Thus a mild case would be one which had erythema and edema but which never had blisters, superficial necrosis, or deep necrosis. A moderately severe case was one which had blisters with or without superficial necrosis but without deep necrosis. A severe case was one which had deep necrosis regardless of the presence or absence of blisters and superficial necrosis. There are obvious faults in this kind of classification. For instance, a veteran may have had severe injury of one toe which developed deep necrosis and was amputated but the remainder of the foot had little if any injury. He would be classified as severe. Examination at follow-up in such a case might reveal much less than in a veteran who had only moderately severe cold injury. The rate of surgical amputation in the three groups was closely related to the severity classification: 0.2 per cent in the mild group, 5.4 per cent in the moderately severe group, and, as expected, 89.1 per cent in the severe group.

Montgomery: That would be digital amputation, would it not?

Simeone: Yes, that is right. The idea that perhaps the criteria for classification may have been reasonable is further supported by the consideration of where these veterans were 4 months after the injury and prior to separation from the service. Seventy-seven per cent of the mild cases were still in the hospital, 88 per cent of the moderately severe cases were still in the hospital, and all of those classified as severe were still in the hospital. Consistent with the data presented by Colonel Blair, the more prominent complaints which were keeping these soldiers in the hospital at this time were these: "painful feet" in about 90 per cent of the cases, hyperhidrosis in 87 per cent of them, tenderness of the skin in nearly 75 per cent, and numbness and tingling in 50 per cent.

It may be well to explain that these data were obtained not only from interviews, laboratory tests, and physical examinations of the

veterans, but also from copies of their medical records Often there were discrepancies between the veteran's statement and the notes made in his record The latter were generally taken to be more nearly correct In about 40 per cent of the cases only a record study was possible A code booklet had previously been designed by Dr Beebe in which could be recorded in code the numerous findings in the history, physical examination and laboratory tests The completed code booklet was readily transferred to punch cards for the statistical analysis No difference was considered significant if, among other considerations it was not at P 05 level or less

Fremont-Smith About this index, this code, was each item given equal weight?

Simeone Yes, for the recording of data, not as an index

Fremont-Smith This is one of the difficulties that inevitably comes in because if all items are given equal weight, obviously they cannot have equal weight and there results an index which has some kind of distortion in it, doesn't it?

Simeone These coded items were not used to compute an index but merely as a standard method for recording information which could then easily be transferred onto punch cards

Fremont Smith In other words, this was used for description?

Simeone Yes

Fremont Smith But not for evaluation?

Simeone When we came to evaluation, it was a clinical evaluation based upon the data obtained in each case, but it did not depend upon the arithmetic of the code numbers

I should like to describe to you briefly the impressions gained from four of the laboratory tests used in this study, plethysmography, capillary microscopy, temperature reactions of the skin and ergometry The data were obtained from veterans such as are illustrated in the following figures

The case shown in (Figure 79) was considered a mild one The picture shows the feet after having been elevated for 5 minutes with the leg at an angle of 30 degrees from the horizontal I would consider this as showing no pallor, others might code the color as slight pallor This is one example of possible center variation

The plantar aspect of the same foot (Figure 80) illustrates the calluses which are common in these men over the metatarsal heads Note the delicate skin underneath the proximal phalanx of the second toes This is the area which is likely to perspire more than normally, to macerate, and to fissure

In the dependent position (Figure 81) the same foot illustrates what I should consider slight cyanosis others might disagree

Fremont Smith Would this depend upon the temperature of the room it is measured in? that is the external environment

Simeone These photographs were all taken at a so called comfortable room temperature between 24 and 26 C

Montgomery How long after the injury were these taken?

Simeone On the average 6 or 7 years

A more severe case with the legs elevated is illustrated in Figure 82 The tips of the toes are actually more pink than normal There is also callus formation and from just looking at this skin hyperhidrosis is strongly suggested One of this patient's principal complaints at this time was hyperhidrosis In the dependent position (Figure 83) there is decidedly abnormal cyanosis of the tips of the toes Again hyperhidrosis is strongly suggested These patients with hyperhidrosis in the affected feet did not have this abnormality in the hands at these examinations Another moderately severe case is shown in Figure 84 which illustrates the desquamation so commonly seen In the dependent position (Figure 85) the skin shows grossly abnormal cyanosis

Figure 86 illustrates a severe case in the elevated position This veteran lost all his toes on the left foot Note the distortion of the toenails and the ulceration of the callus over the head of the fourth metatarsal bone He also had calluses and fissures on his heels and severe hyperhidrosis

Montgomery Was that patient walking all right?

Simeone Yes but he had severe symptoms He was at work Figure 87 shows the same subject with the feet in the dependent position

PLETHYSMOGRAPHY

The Burch Winsor (1) digital plethysmograph was used The data were collected analyzed statistically and submitted to Dr George E Burch and Dr C Thorpe Ray who had the responsibility for describing and interpreting them Since both limbs were nearly always involved in the cold injury these veterans could not serve as their own controls However in a previous study of veterans of World War II who had incurred wounds of the arteries considerable plethysmographic data were obtained for normal digits in a comparable population These were used as controls with which the data from veterans who had incurred cold injury could be com

pared Dr Burch and Dr Ray found that when the absolute value obtained from veterans who had incurred cold injury were compared with those from normal subjects under the different conditions tested no statistically significant differences could be found between the two groups

Fremont Smith Were they put under any stress conditions?

Simeone Yes the stress conditions" were as follows Measurements of the size of the pulse wave were made in a comfortable environment of 24° to 26°C and recorded as cubic millimeters per 5 milliliters of part as described by Burch (1)

Montgomery Were these patients lying flat?

Simeone They were lying flat The toe was approximately at the level of the right auricle

The ambient temperature was then changed to from 90° to 95 F hot room and similar measurements were recorded after an hour in such an environment Again when these findings were compared with those obtained in the controls no statistically significant difference was found The veterans were then exposed to a cold environment (65 to 70°F) The low pulse volumes at this low ambient temperature did not differ from the controls In addition after having stabilized at these temperatures reflex vasodilatation was induced by the method of Gibbon and Landis (2) and vasodilatation was also induced by procaine block of the posterior tibial nerve The change in pulse volumes between the values in the cold room and those after reflex vasodilatation and after nerve block did not differ significantly from the values obtained in the normal controls The lack of heterogeneity between the control group and the veterans who had incurred cold injury could easily be caused by center variation in the details of performing the tests and therefore in the data obtained One cannot say therefore that if done under truly identical conditions in all centers the plethysmographic data would not have been discriminative

Fremont Smith Was the rate of change measured?

Simeone No the rate of change was not measured Nor unfortunately was the rate of change studied in the tests of temperature reactions in the skin

Blair Do you have any record on how many of the patients may have had sympathectomies?

Simeone Sympathectomized patients are excluded from the comparisons mentioned I was not going to talk about the veterans



FIGURE 79



FIGURE 80



FIGURE 81



FIGURE 82



FIGURE 83

FIGURE 79 Feet late after cold injury elevated and essentially normal in color mild injury

FIGURE 80 Same subject as in Figure 79 callus formation is shown

FIGURE 81 Same subject as in Figure 79 with legs dependent slight cyanosis is

FIGURE 82 Moderately severe cold injury legs elevated tips of toes are pink and there is formation of callus and hyperhidrosis

FIGURE 83 Same subject as in Figure 82 with legs dependent cyanosis is shown



Figure 84

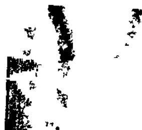


Figure 85



Figure 86



Figure 87

Figure 84 Moderately severe cold injury, feet elevated, desquamation of skin is shown

Figure 85 Same subject as in Figure 84 feet dependent, cyanosis is shown

Figure 86 Subject after severe cold injury, legs elevated some of toes amputated abnormality of nails and formation of calluses and fissures are shown

Figure 87 Same subject as in Figure 86 with legs dependent cyanosis is shown

with sympathectomy at all In actual numbers perhaps some sixty veterans had had sympathectomy Attempts to correlate the plethysmographic findings with the type of cold injury the severity of the injury and other characteristics proved unsuccessful

CAPILLARY MICROSCOPY

Capillary microscopy also proved disappointing as a means of characterizing cold injury Capillaries were examined in the nail fold of the toe a fraction of a millimeter proximal to the cornified edge on the nail and were photographed While techniques have been described for digital capillary microscopy and photographs of capillaries in the nail folds of the fingers have been published we had not éncountered photographs of capillaries in the nail folds of the toes A monocular compound microscope was used with an Ultropak lens and a Leica Micro Ibso attachment Cedar oil or mineral oil was used on the skin in contact with the lens The capillary loops were observed and described by means of a 6 volt lamp Selected fields were photographed by means of a stroboscopic flash The most distal bank of capillaries was usually studied and photographed because these could be observed lengthwise instead of on end

These are examples of the photographs that were obtained (Figures 88 91) Represented in Figure 88 are essentially normal capillary loops One loop is shown which we thought illustrated slight widening of its venous end In Figure 89 are shown capillaries before (*A*) and after (*B*) posterior tibial nerve block with 1 per cent procaine The capillaries become more prominent and easier to see and to photograph but their general morphology remains unchanged Venous occlusion also made the capillaries appear more prominent but the gross morphology remained unchanged Diagrammatically the following types of capillaries were seen (Figure 90) Normal hairpin loops are represented in (*A*) Some seemed to cross but it is not possible to be certain that the limbs of the loop were not being seen sidewise and in fact were not crossing We considered unusually large loops an abnormality (giant loops" in (*B*)] Some loops with cross connections we thought were abnormal and very fine tenuous loops (fibrils") were interpreted as being newly formed capillaries but this was only an impression Some loops turned and twisted formed clover leaves and resembled glomeruli (*C*) and (*D*) These last were thought to be the most abnormal

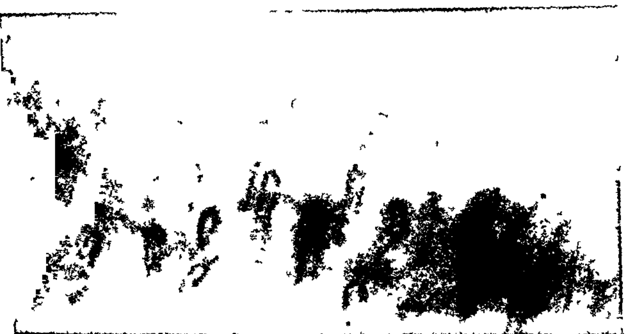


FIGURE 88 Essentially normal cap llaries na l fold veteran with m ld cold nj ry twists and interrup ions of blood column in cap llary loops are shown



FIGURE 89 Capillary loops before and after block of posterior tibial nerve

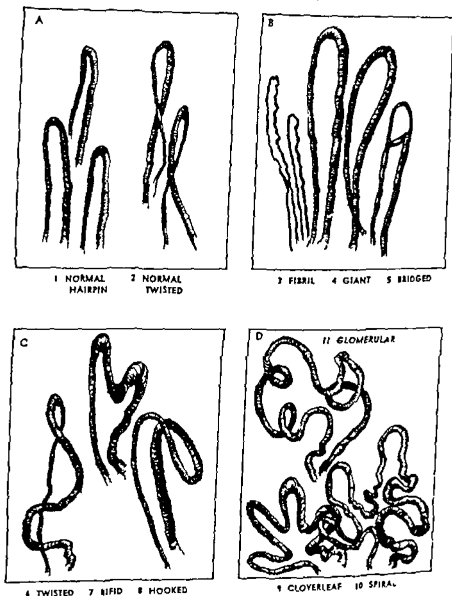


FIGURE 90 Varieties of capillary morphology

Fremont Smith Would you say that the grossest things about those abnormal ones is that they are very much longer?

Simeone And they are twisted and tortuous

Fremont Smith They have to twist and contort because if they are going to become longer by the same token they are going to twist

Simeone Figure 91 shows some capillary loops that are within normal limits Here is shown segmentation of the column of blood within the capillary loop itself and these are collecting venules across the bed

In the Cleveland center we studied forty eight veterans in this manner or ninety six extremities The anatomic appearances of the capillaries were graded from normal to severely abnormal When these findings were related to the severity of the clinical status at follow up or to the severity of the initial injury there was a suggestion that highly abnormal capillary forms were found more frequently among the more severely injured veterans However we studied nine normal individuals of the same age group (18 feet) and were discouraged to find a high proportion of highly abnormal capillary forms in the nail folds of apparently normal toes Therefore in the absence of adequate information on the distribution of the varieties of capillary loops in the nail folds of the toes it was not possible to establish a relationship between capillary morphology and the existence or severity of cold injury

Montgomery Vasoconstriction and vasodilatation didn t change their total loop shape?

Simeone The normal individuals?

Montgomery Yes

Simeone They did change with posterior tibial nerve block The loops appeared dilated after the vasoconstrictor paralysis They were more prominent and easier to photograph

Montgomery It did not change their total loop shape?

Simeone No their general morphology did not change The failure to correlate clearly the unusual capillary forms to the presence of cold injury and its severity was disappointing Possibly unlike the nail folds of the fingers those of the toes normally contain such bizarre capillary forms or possibly our normal subjects may have had some injury to their toes in years past whether as the result of cold or from other trauma

Fremont Smith Are there any data on toes of children?

Simeone Not that I am aware of



FIGURE 91 Capillary loops with collecting venules Interruption of column of blood and intermittency of flow in one loop (arrow)

SKIN TEMPERATURE

Dr William W L Glenn interpreted the data obtained from studies of the skin temperature The tests were conducted as they were for plethysmography In fact they were usually done at the same time For normal controls the data obtained from the examinations of normal limbs in veterans who had incurred arterial injuries were used It was found that when the subjects were exposed to a cold environment the skin of those with cold injury cooled much more slowly than that of normal limbs This is reminiscent of the toes of individuals with vascular disease other than cold injury They often cool more slowly than normal subjects

Montgomery How cold was the environment and how long were they exposed to it?

Simeone For 60 minutes for the most part at temperatures of 68° to 69°F Some may have been studied at temperatures as high as 72°F and some as low as 65°F

Fremont Smith They cool more slowly

Simeone They cool significantly more slowly that is right

Blair How much clothing did they have on?

Simeone A loin cloth

Blair No meal?

Simeone Insofar as possible these tests were done in the morning in a fasting state but I doubt that all of them were

Montgomery Naide and Sayen (3) in our laboratory have found that the fingertips of half of the normal subjects in a room at 68°F (20°C) cool to 77°F (25°C) In general more severe vasoconstriction occurs in toes

Simeone This is 60 minutes though

Horvath Toes ordinarily cool a little faster than hands

Simeone Dr Glenn studied still another test of the behavior of the temperature of the skin

Fremont Smith One point might be mentioned there I suppose certainly with the normal subjects the more anxious they were the more rapidly they would cool I know this is true of the hand and I assume it is true of the toes also perhaps to a lesser degree I do not know if anyone can corroborate that or not This was shown by Mittelmann and Wolff (4) and they precipitated sharp drops in skin temperature by discussing with the subject anxiety provoking situations They were able to obtain vasoconstriction in a room that was less cool if there was an anxiety

provoking discussion in some of the subjects even the presence of the doctor was enough to precipitate a drop in temperature and in patients with Raynaud's disease of course there was vaso-constriction in the fingers that was much more profound than in normal subjects whether they were exposed to a cold environment to an anxiety provoking situation or to a combination of both

Simeone Actually if the veteran saw one of us handling a needle and syringe and suspected that an injection was planned the temperature of the skin would come right down

Fremont Smith If this was the case was it possible by such measures to cool the cold injured men rapidly with emotional tension or were they resistant to such cooling?

Simeone They would cool faster during the excitement but interestingly enough both the normal subjects and those with cold injury would often return to the level at which they would have been if there had been no excitement

Fremont Smith When the anxiety was gone?

Simeone Yes and Dr Glenn found that two other indices of changes in skin temperatures differed between the normal controls and the veterans with cold injury These were the difference between the temperature of the skin in the cold room before and after vasoconstrictor activity was interrupted by means of posterior tibial nerve block and the difference between the temperature of the skin in the cold room before and after reflex vasodilatation by the method of Gibbon and Landis (2)

In the normal subjects plotting the difference in temperature against the cumulative percentage that attained that difference after nerve block a steep curve is obtained with less than 15 per cent showing a difference no greater than 9.7°C 80 per cent showing a difference between 9.7° and 15.7°C and 5 per cent showing a difference of from 15.7° to 19.7°C By contrast in the veterans with cold injury the comparable percentages were 54.2 45.6 and 3 Comparable figures after reflex vasodilatation were 18.2 78.8 and 3.0 and 37.0 61.5 and 1.5 respectively

Fremont Smith The height of the curve is the degree of rise in temperature — in degrees of temperature?

Simeone No the height is the cumulative proportion or percentage of cases that reached the designated increment in temperature or lower

Fremont Smith And that difference in temperature is a difference in rise isn't it?

Simeone That is right

Fremont Smith So this means they rose that much? They reached a height of increase of that much?

Simeone That is right These two indices describing the behavior of the temperature of the skin are probably the most significant with regard to differentiating the normal from the injured and even the different degrees of injury If you are interested the following are the absolute mean values reached not the rises from basal by the subjects with mild moderately severe and severe injuries respectively 33 4° 32 7° and 28 8°C The differences between these two groups are significant at the P< 05 level

Horvath That is between the mild and the severe?

Simeone Between the mild moderately severe and severe

Horvath That is each one of those have that level of significance?

Simeone Yes

Montgomery The injured ones then have only a moderate capacity for vasodilatation?

Simeone The following figures represent the differences between the temperature of the skin at maximal vasodilatation and that at basal vasoconstriction in the cold room The mean differences were 9 3° 8 3 and 4 6°C respectively for the initially mild moderately severe and severe cases In a one tailed test of significance these figures were significant at the P 01 level

Shumacker What about the normal subjects do you have those figures?

Simeone I can give them

Montgomery The normal temperature of the toe during vasodilatation would be about 32°C in a 20°C (68°F) room

Simeone The mean normal in our group would be about 33°C for maximal vasodilatation

Montgomery They have some vasomotor paralysis and also some reduction in capacity for blood flow? So full vasoconstriction does not occur and full flows during vasodilatation do not occur?

Simeone The mean temperature reached in the cold room by the veterans with cold injury was 23 5°C The normal controls reached a mean temperature of 21 5°C The difference between these actual values was not statistically significant

Burton So Dr Montgomery s question was that these patients when put in a cold room did not constrict as much as a normal

subject, and when put in a warm room did not dilate as much as a normal subject, is that true?

Simeone Yes, that is right

Burton What was the level that the normal subjects reached in dilatation, as in nerve block or full reflex dilatation?

Montgomery It was 32

Simeone The mean level reached by the normal controls after nerve block was 33 5°C

Fremont-Smith Almost the same as the mild

Montgomery And once more the room temperature in Centigrade and given in Fahrenheit?

Simeone About 20° or 21°C, on the average

Montgomery Do you conclude that the more severe ones have more arterial occlusion? I think it is fair to conclude that isn't it?

Simeone Possibly, but I am not sure The most interesting thing about these subjects actually was the difference between the cumulative percentage curves in the two groups, normal and injured (Figure 92)

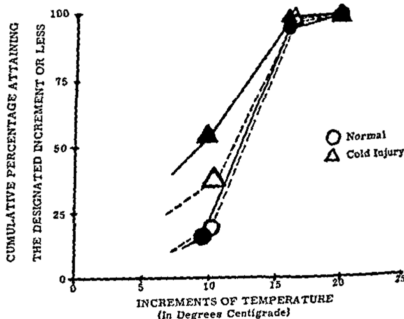


FIGURE 92 ... ment ... nd
of temperatu[illegible]
temperature [illegible]

Horvath There is a better way of plotting these two curves A cumulative frequency plot on a log basis can be used I think if the plot is on a log basis the curves would have been shown to be similar It looks as though there are five points which are on the verge of being statistically questionable as to occurrence of any real difference

Simeone I cannot answer the point raised offhand except to say that these data have been subjected to very rigorous scrutiny from the statistical point of view

Horvath Certainly there would have been a potential value in determining the equilibrium temperature Did they ever attain an equilibrium temperature?

Simeone Eventually they do come down in the cold room if kept there long enough but the normal subjects come down much more quickly than those with cold injury Dr William Glenn suggested that our veterans with cold injury even this long after exposure may have some element of deficiency in sympathetic vasomotor control not a sympathetic paralysis but an insufficiency

Montgomery Including perhaps some damage to vasodilator fibers if there are vasodilator fibers to the skin of human limbs and a slight degree of arterial occlusion?

Simeone Yes possibly although the existence of vasodilator fibers in the skin of the human extremity is seriously questioned

Fremont Smith And there is also the element of perspiring to be considered which will add to the drop in temperature and will vary with the atmospheric conditions not just temperature but moisture conditions of the room

Simeone Yes

Fremont Smith Any movement of air which will cause more rapid evaporation is a factor to be considered

Simeone Air movement is another variable in our studies It was hoped that all our constant temperature rooms would be nearly identical but actually there was variation from center to center

Shumacker Dr Simeone certainly in spite of the variables you mentioned the difference between an average rise with nerve block to 29 4 C in the severely injured group and to 33 5°C in the mildly injured and in normal subjects must be significant Nerve blocks have been done by so many investigators for such a long period of time that we know quite well that a rise to this level does occur normally and it must be significant that the digits of the severely

injured group failed to reach this temperature after nerve block even if the basal atmospheric conditions were not always precisely the same

Simeone Yes that is true

Montgomery If this difference is the rule it is an important observation This is a large difference in blood flow In a room temperature of 23°C the flow is some four or five hundred per cent greater in a toe that has a skin temperature of 33°C than in one having a skin temperature of 28°C

Simeone Yes and especially at that level of temperature

Burton I suppose it was not practical but it does seem to me a pity that while you had these plethysmographs and fitted them up you did not do venous occlusion plethysmography Obviously there must have been very large differences in the blood flows although this did not show up in the size of pulsation (which is not surprising)

Simeone Yes we do regret that rates of blood flow by the venous occlusion method were not recorded in these cases

ERGOMETRY

The value of ergometry in studies such as this is another controversial matter Each of the centers built an ergometer from the same basic plan but with inevitable minor variations There was some center variation therefore but surprisingly not as much as I thought there would be The ergometer consisted simply of a five gallon carboy fitted with a stopper through which passed two tubes one connected to a mercury manometer and the other to a rubber bulb The rubber bulb was attached to a frame in such a manner that an overlying pedal could compress it To the pedal and frame were attached electric contacts which closed a circuit containing a light bulb when the rubber bulb was completely compressed Appropriate valves permitted the passage of air only from the rubber bulb to the carboy The subject sat in a chair of such a height that the distal part of the thigh did not rest on the chair The fulcrum on which the bulb compressing pedal rocked was in line with the ankle joint It was felt that most of the work was accomplished by the calf muscles and the intrinsic muscles of the foot The quadriceps and hamstrings stabilized the knee The apparatus was set up so that on a revolving drum were recorded the actual strokes completion of each stroke the pressure developed in the manometer the time and signals referable to the development of discomfort and fatigue In this manner the injured leg was tested

and compared with the performance of the uninjured leg When the hands were tested the rubber bulb was compressed in the hand instead of by the pedal With each compression 30 ml of air were forced into the carboy The rate of compression was controlled by a metronome and was kept constant We were interested in recording the total pressures developed the duration of the exercise and the time of development of fatigue and of the symptoms which forced the subject to abandon the exercise As a matter of fact I believe we got the ideas for constructing this type of ergograph from Dr Shumacker

Shumacker We used a similar apparatus during World War II in order to study fatigue in the upper extremities

Simeone We used the apparatus in the veterans with arterial wounds to test the injured limb against the normal one In the veterans with cold injury both limbs were affected so that the subject could not serve as his own control We used as control therefore the data from the normal limbs in the arterial injury study the populations being similar except for the type of injury

Montgomery Where is the pressure of air in the bulb during compression and is the patient sitting or standing?

Simeone The subject does the test in the sitting position The pressures developed varied considerably but in the veterans they averaged about 650 mm Hg for the uninjured leg and about 250 mm Hg for the uninjured hand

Fremont Smith What was your end point when he stopped?

Simeone When he could go no further because of discomfort

Fremont Smith And that was his statement?

Simeone That is right he gave up

Fremont Smith Did he give up because of pain or just give up?

Simeone The normal subjects and the veterans who had incurred arterial wounds gave up because of deep seated pain or ache in the calf muscles in the ankle or in the quadriceps tendon The location of the pain varied in different individuals In my own case I gave up because of pain in the quadriceps tendon In the case of the veterans with cold injury some gave up because of burning pain in the sole of the foot some because of pain or ache deep in the foot and others merely stated "I am so tired I can t go any further

Some of the data are shown in this graph (Figure 93) It shows the distribution of veterans with cold injury plotting numbers of

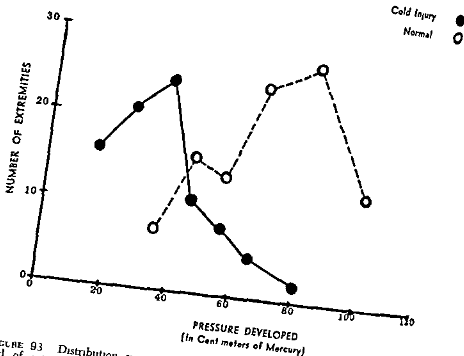


FIGURE 93 Distribution curves of ergometric performances of control extremities and of extremities after cold injuries Ergometric pressures were developed by normal lower extremities of veterans with arterial wounds on the contralateral side (control studies) and by limbs of veterans with cold injury

cases against the pressures developed The peak for the veterans with cold injury is at 35 cm Hg for the control limbs 80 cm Hg We thought these controls were the best we could possibly get because they were of the same age the same sex and had the same motivations

Fremont Smith At least you could say they were subject to the same motivational problems

Sweet Actually the motivation for the man with arterial injury might be to show what a magnificent limb he has on the normal side and how much worse the performance is on the side of arterial injury, so that I think that was perhaps a less satisfactory control group than just the man on the street

Simeone That is a possibility

Horvath Did you offer them a prize for the amount of work they could do?

Fremont-Smith Compensation for the work they couldn't do?

Horvath That is a prize in the opposite direction, but was a prize offered in either direction?

Simeone No With the arterial injury group, however, we were able to compare the performance of their uninjured hands and feet with that of normal individuals, and they matched very satisfactorily

Horvath We used the same technique in students, and the variability among the medical students is I am sure, in the neighborhood of from 300 to 400 per cent

Simeone There is a great deal of variability in this type of performance, of course, and that is why we must depend on statistical considerations to keep us straight

Fremont-Smith That is a somewhat forlorn hope, isn't it Dr Simeone?

Simeone In our own study center, the average pressure de-

comfort, or fatigue, was 233 seconds for the former group and 146 seconds for the latter The total duration of the exercise averaged 787 seconds for the normal controls and 394 seconds for the veterans with cold injury These differences were significant at a better than one per cent level As Dr Horvath mentioned there is a great deal of variability in these tests but one would expect and hope that the statistical analysis would take the variability of the data into account

Horvath Statistics do not take into consideration motivation

Fremont-Smith The problem of measuring fatigue in uninjured people has so far been an impossible one to solve I do not think we know how to do it and therefore we should all be very appreciative of your difficulties in trying to study fatigue in injured people because this is infinitely more difficult

Simeone That matter was considered very thoroughly in the deliberations on this problem We considered having a neuropsychiatric evaluation of each one of our veterans but that was impractical We compromised by testing each veteran by the Cornell Index I do not know what the results of that evaluation will be, but I have the impression that it will not alter the interpretation of the data as described

Montgomery If the injury was almost all foot there was a little bit of ankle injury wasn t there?

Simeone In some of the cold injuries yes

Montgomery In this system the power is provided mostly by the calf muscles and some by the thigh muscles In controls failure results from fatigue in these muscles In subjects with cold injury exercise of the injured muscles of the foot may have led to failure before the other muscle groups developed pain

Simeone That is right *the controls and the subjects with cold* injury differed with respect to the location of the discomfort which led to discontinuing the exercise It is important that the development of pain in the foot was a limiting factor in the veterans with cold injury and not in the normal controls

Tremont Smith But as you said sometimes the pain was up in the quadriceps so the fatigue was there

Simeone Yes but that was the case in the normal extremities In the injured the causes for stopping the exercises were tiredness" or aching in the calf or ankle and more commonly pain in the foot

Horvath Have you any idea as to the amount of work done by the normal group over the same period of time that the cold injured group were working?

Simeone Calculated as actual work done?

Horvath In the same schema that you have employed For instance in the injured group a pressure of 35 1 cm Hg was developed and the time interval was 146 seconds How much work was done by the normal group in 146 seconds?

Simeone I do not know

Horvath Roughly they look about equal

Simeone I think you would expect them to be equal since both groups followed the metronome and for the most part completely compressed the rubber bulb with each stroke

Horvath Then the significance of the difference would be decreased

Sweet Not necessarily at all

Montgomery The work done in unit time was *equal but the* failure to continue work occurred sooner in the injured group?

Horvath Yes

Behnke They followed a metronome didn t they?

Tremont Smith But they did not push it all the way down

Montgomery The plantar muscles of the foot were responsible for the plantar intermittent claudication whereas the main power is from the calf which is above the site of the injury

Simeone Actually since they were exercising at a rate controlled by the metronome and we know they did complete every stroke or nearly every one the work performed by the injured and uninjured for a comparable time would be the same

Fremont Smith I thought you said they did not necessarily push it down

Simeone They did as a rule and the completion of each stroke was recorded on the kymograph

Fremont Smith You asked them to push it down until it clicked in each instance?

Simeone That is right In fact they turned on a little lamp which they could see when the stroke was completed by pushing the pedal down far enough

Fremont Smith Did they know how much the manometer was going on what the pressure would be?

Simeone No they couldn t see that because all of the recording apparatus was on the opposite side of the table

Fremont Smith What about the reliability of the measurement for the same individual repeating it four or five times?

Simeone With our veterans we didn t have the opportunity of repeating the test four or five times The test did prove quite reliable for normal subjects whom we studied So much so that it was easy to pick the right hand from the left in the records Handedness had little or no influence on the performance of the leg but it did have an effect upon the function of the hands

Montgomery Most of the severely injured of these patients did have pain in their feet?

Simeone Yes

Montgomery Was it possible to be sure that a large proportion of them had true plantar intermittent claudication?

Simeone It is possible that the veterans did have true plantar intermittent claudication but it is very difficult to be absolutely certain

Montgomery It was your impression they really did have that as part of their pain?

Simeone I couldn't be certain that what they had was intermittent claudication Possibly they may have had pain from ischemia of the plantar skin in the foot

Montgomery No but worse after a certain distance of walking not just a constant pain at all times?

Simeone Yes that is right The pain was not constant in the feet except in a small proportion of the veterans

Montgomery That would all fit in with intermittent claudication

Burton This is a very minor point but are you sure these are centimeters of mercury? You see 67 cm Hg is a very high pressure

Simeone Yes they are centimeters One of our technicians a woman was able to pump well above that figure and indeed had to be stopped to avoid having the mercury go over the top of the manometer She was exceptional

Burton That is nearly an atmosphere of pressure I should think the bottle would blow up

Simeone We were well aware of that and as a matter of fact both the bottle and glass manometer tube were taped

Horvath Did you try stimulating the nerve?

Simeone No We thought of the possibility of doing ergometry by that technique as Landis described it (5) but we did not adopt it in the interest of not alienating the subjects The test can be a little uncomfortable

Montgomery Isn't this the first report of intermittent plantar claudication in cold injury?

Simeone If it is intermittent claudication I am not entirely certain of that

Montgomery What is it?

Simeone I do not know Possibly it represents ischemic pain in other than muscle tissue in the sole of the foot

Montgomery How long did it linger after the end of the test or after the end of walking?

Simeone I do not know the answer to that

Montgomery Did they get relief rather promptly after stopping the exercise? Did they look as if they were relieved of pain shortly after stopping the exercise?

Simeone We have no data on the duration of the discomfort When I have performed the exercise myself I have had my main

mum discomfort in my quadriceps tendon This discomfort has lasted several hours, and not only a few minutes as it does in the case of intermittent claudication

To summarize our work, the clinical appearance of the feet of veterans who incurred cold injury during World War II is illustrated by means of color slides, some of which are reproduced herein Most of the data collected from the follow-up studies of the veterans are still in the process of interpretation When completed, they will probably be published in the form of a monograph from the Veterans Administration by personnel of the five centers who performed the studies Preliminary data regarding some of the tests performed are presented in summary form Plethysmographic studies proved to be nondiscriminative but it is emphasized that this should not necessarily be interpreted as evidence that there are truly no plethysmographic changes in late cold injury, but rather a reflection of the method by which the data were obtained Capillary micrography revealed bizarre capillary forms in the toe nail folds of veterans with cold injury, but similar forms were found in the nail folds of the toes of normal subjects Late after cold injury the responses of the temperature of the skin suggested that the blood vessels of the skin did not constrict as effectively as the normal ones do when exposed to cold and did not dilate as effectively when vasoconstriction was inhibited or blocked The ergometer did differentiate the veterans with cold injury from the performance of normal extremities It is recognized however, that motivation is an important problem in this regard, and a most difficult one to evaluate

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RESUSCITATION OF HYPOTHERMIC, SUPERCOOLED, AND FROZEN MAMMALS*

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R K ANDJUS
Department of Physiology University of Belgrade
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Smith In this field of resuscitation Dr Andjus in Belgrade had succeeded in doing something that no one had done before i e reanimating ice cold rats and he had done it by heating the heart He used a little metal spatula which he heated in a Bunsen flame and then clapped onto the precordium With that method the fur and the skin were burned Nevertheless Dr Andjus revived 20 per cent of the rats and they recovered and survived (1) When he came to us we repeated this and the Mill Hill rats were like the Serbo Croatian rats one in five could be reanimated by this method But we felt that if one in five could be reanimated five out of five could be reanimated

Dr Andjus and I then worked together for 3 months and developed another method where we shone a bright light onto the chest wall It was a light from a projection lamp and as that had better penetrating power we were able to revive 44 per cent and eventually 65 to 75 per cent of the rats so that they survived long periods (2 3)

Then I retired from work on rats because it was quite clear that something better was needed Dr Andjus and Dr Lovelock collaborated and developed the use of the magnetron which we already had in the department Dr Lovelock and Mr Perkins had built it previously for instant thawing of specimens of cells and tissues frozen at −79 C Dr Andjus will describe some of the interesting experiments he did using the magnetron with which he could revive from 80 to 100 per cent of the ice cold rats

Andjus The magnetron generates centimeter waves and they can be focused at a relatively small area My idea was to apply

*Prepared at the National Institute for Medical Research London England

heat locally to the animal's chest (1) When dealing with a larger animal the monkey, the penetration of microwave rate was not sufficient, so we used a more conventional diathermy by means of which it was again possible to heat just the thorax

Horvath Were these 10 cm waves you used?

Andjus Yes, as far as the magnetron was concerned

Horvath What power?

Andjus I can't give you the correct figures offhand

Smith We can give them to you later (4)

Horvath The basic difficulty that we find in the use of any of these microwaves is that they penetrate through the tissue and heat at a depth which is dependent a bit upon power and also dependent upon the wave length that is, the smaller wave length will penetrate a little deeper But the surface is not heated

Smith No that was the idea

Horvath Primarily the tissue is heated I know several people have made an attempt to heat the heart by this means but have never succeeded in the intact animals

Smith That was where Dr Lovelock, together with Mr Perkins who is our electronics expert ingeniously succeeded

Fremont Smith Do you mean that you find you do not need the special heating of the heart first for the larger animal?

Smith No it is not necessary There is one thing I would like to mention and that is the psychological studies on the survivors of this freezing We did this work in collaboration with Professor Russell and Dr Knopfelmacher of the Department of Psychology at University College London They trained rats to run in mazes and to do tests involving swimming then Dr Andjus took the animals once again cooled them and revived them Next Russell and Knopfelmacher retested them for their ability to solve new problems

Quite briefly the results were as follows There was no appreciable impairment of memory but there was a temporary reduction in the capacity to learn new problems

This reduction in learning capacity was only temporary and became less pronounced during the weeks that followed resuscitation and convalescence

We were very interested in this result because it was not consistent with the theory that memory depends on a continuous passage of nerve impulses or maintenance of some kind of dynamic

active metabolic process in the neurons within the brain Hitherto this has been one of the favorite theories to explain how memory is achieved (5)

I would like Dr Andjus to tell you about the experiments when he cooled rats repeatedly and down to body temperatures just above zero and reanimated them I would also like him to tell you about some of his work on kidney function in hypothermic rats

Fuhrman Dr Smith does your work on the psychological effect of cooling correspond to that of Gerard?

Smith Gerard (6) and his colleague Ransmeier (7) cooled their hamsters only to +5°C and they never arrested the heart or the circulation By contrast in our experiments with the rats and the hamsters breathing and heart beat were completely at a standstill Gerard (6) and Ransmeier (7) recorded electroencephalo grams and they were able to show that at +5°C there was no electrical activity in the brain Nevertheless memory was not im paired showing that it did not depend on cerebral activity We therefore do support Gerard very strongly in this matter that memory does not depend on a dynamic process We have cooled our animals to lower temperatures than they did We think we have arrested all active processes within the brain

Fuhrman Didn t they find that the hypothermia reduced the rate at which the animal was able to find his way out of the maze?

Smith No

Fuhrman I thought that if the time between learning to run the maze and the cooling was just right it did reduce the rate at which the animal got out

Smith If they were cooled too soon after learning immediately after learning then they did show a reduction We did not do that as I explained Dr Knopfelmacher and Professor Russell had the rats for a week or two first then we took them back and so there had been a decent interval since training They had a really thorough training before we got them

Fuhrman The point was that there is a certain interval which is critical

Smith It was a very short interval

Fremont Smith I would like to make one point here I think it is generally true that memories of short duration are much more vulnerable and that vulnerability increases with shortness of dura tion or that invulnerability or protection of memory increases with

time This is a very important general phenomenon and I am very interested It came out in Gerard's experiments In other words if the learning process had been allowed to be imbedded more deeply over time, then it was less vulnerable to the freezing and that is true of all kinds of trauma In a hit on the head, the memory loss is always for the more recent events, the ones for which the memory has had the shortest duration

Smith It was a matter of minutes in their experiments not a matter of days, Dr Fuhrman The interval between training and cooling had to be less than 5 minutes in order to produce an effect

I think we have more than confirmed the views of Dr Gerard and Dr Ransmeier, because the electrical activity in the rat brain is suppressed at body temperatures below 18°C That was shown quite conclusively by Horsten (8) and Lemaitre (9) In Dr Andjus's rats, cerebral activity was probably arrested for from 1½ to 2 hours during the entire time they were below temperatures of 18°C We kept our animals cold much longer than Ransmeier and Gerard did and nevertheless they showed no significant loss in memory after resuscitation

Fuhrman That is very interesting

Smith Yes I had never come in contact with the animal psychologists before and it was an interesting experience for me to see something of their work and something of their problems too

Simeone Dr Smith, do I understand correctly that frozen hamsters developed no edema of the frozen parts when they were reanimated?

Smith Only under special experimental conditions, but I would like to give Dr Andjus a chance to talk to us because he is the originator of this work on resuscitating animals and we at Mill Hill owe him a great deal

Andjus First of all, I would like to tell you that the possibility of recovery after cooling to body temperatures below zero is not just a peculiarity of hibernating animals and hamsters I was able to reanimate rats after reducing their central temperature below zero down to −3°C in the colon and about −5° to −6°C under the skin (10) Those animals that supercooled were reanimated and recovered completely None of the animals that underwent crystallization however, was so far among the long term survivors

Smith I should explain that at this point Dr Andjus returned to Belgrade, but it is possible that if he had used the diathermy,

which I will describe later, he would have succeeded in reviving partially frozen rats

Andjus I had used the magnetron microwave generator for reanimating them and I was not able to get complete recovery when dealing with frozen rats As a matter of fact, they can be reanimated but they die soon afterward This was, however, a very small series The possibility of recovery after freezing, partial freezing at least, cannot be ruled out on the ground of these experiments

After this method of rewarming by microwaves was established the first thing I wanted to see was what the influence of the time factor was, what the time limits were for reanimation Figure 94 shows the results of a series of experiments on animals kept for different lengths of time at zero, it shows that ten out of ten animals were long term survivors when they were kept in suspended animation for from 60 to 70 minutes The black blocks show the long-term survivors, the shaded areas show the number of secondary deaths

When the time during which rats were kept in suspended animation was prolonged the survival rate decreased and after 120 minutes I could not obtain any long term survivors

Dugal That is for rats?

Andjus That is for rats

Dugal How about monkeys could you keep them at that temperature for an hour and reanimate them?

Andjus Yes, one was cooled to 5°C and was without heartbeat for about 1 hour

Fremont-Smith What age rats were these?

Smith They were about 8 weeks old They are adult rats

Andjus They were about 200 grams heavy Figure 95 shows some results of repeated cooling in rats On these graphs, body weight is plotted against time One rat was cooled every second day to 0° and during the cooling period growth was arrested, after the seventh cooling this animal died On the same figure another experiment is illustrated which shows that if there is a delay between two consecutive coolings long enough in order to allow the animal to regain its initial weight then the animal can be cooled repeatedly up to ten times to 0° and it remains capable of resuming growth afterward

In the experiments shown in Figure 96, I have seen something like an adaptation produced by repeated cooling First of all the

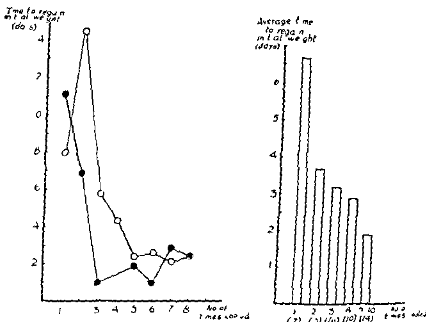


FIGURE 96 The effect of repeated cooling on recovery of weight (*A*) results obtained in two different rats (white and black circles) (*B*) average values from larger groups of animals Number of animals indicated in brackets

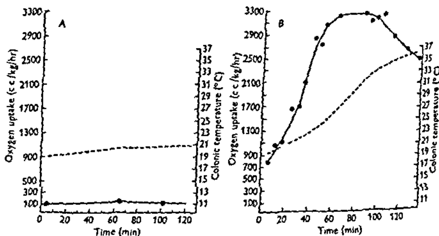


FIGURE 97 The oxygen consumption and colonic temperature of two rats left at room temperature (20°C) (*A*) previously cooled to 2°C and rewarmed to 15°C (*B*) previously cooled to a colonic temperature of 15°C ● oxygen consumption ---- colonic temperature Reprinted by permission from Andjus R K, and Smith A U Reanimation of adult rats from body temperatures between 0 and +2°C *J Physiol* 128, 446 (1955)

animal is cooled to 0 C and then reanimated and rewarmed to 15 degrees of body temperature and left at room temperature spontaneous rewarming will not occur The oxygen consumption rate remains low all the time until death occurs (3)

Smith These being rats as opposed to the hamsters

Andjus Yes that is a difference In the reanimated rat left at room temperature oxygen consumption remains very low Body temperature does not go much above the room temperature and the animal dies after a few hours if it is not rewarmed artificially

Figure 98 shows the increase in body temperature above the room temperature level in rats cooled to 0 C the reanimated rewarmed to 15°C and left at room temperature In the animals cooled for the first time to zero it is evident that the body temperature does not go spontaneously above the room temperature but after the sixth and seventh cooling the rat can rewarm spontaneously from 15 C upwards and regain its normal body temperature (10)

Tracell Does it shiver?

Andjus It does shiver If you rewarm a rat after cooling it to zero rewarm it to normal body temperature in a hot water bath and then leave it in a refrigerator at about 0 degrees of ambient temperature the body temperature of the reanimated rat will fall steadily The rat is poikilothermic This is true however of rats cooled and rewarmed for the first time Animals rewarmed for the sixth to seventh time are able to keep their body temperature at normal level when placed in the refrigerator (10) This is something of an adaptation developed by repeated cooling

Tracell How long does that adaptation last?

Andjus That I do not know

Lewis Could you tell us something about the carbon dioxide content in those jars when you cool the rats?

Andjus Yes I can At the end of cooling the concentration of carbon dioxide is from 15 to 16 per cent and the concentration of oxygen is from 3 to 5 per cent

Burton Could you tell us why you put the animals in the jar and leave them for one hour and then take them out and use another method of cooling? Is it just based on experience did you just try this and find it worked? Why not leave them in the refrigerator all the time?

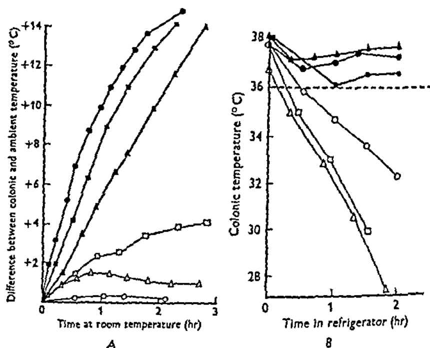


FIGURE 98 Body temperature in recently reanimated rats (A) The rise above room temperature of the colonic temperature of rats previously cooled to 0° re- animated rewarm ... ○ △ □ ... ● ■ rats ... rats reanimated ... ▲ ... s put in a ... reanimated for ... for the first ... refrigerator (0° ... h t n c ● ... time ■ a rat r ... ▲ a rat revived for the seventh time Reprinted by permission from Andjus R K Suspended animation in cooled supercooled and frozen rats *J Physiol* 128, 547 (1955)

Andjus If the animal is kept in air above zero in the refrigerator all the time then a long time is needed to cool it from 15° C down to 0 degrees because the temperature gradient becomes smaller and smaller I thought that it would be much safer to cool the animal as quickly as possible in that range from 15°C down to 0 degrees because the heart stops beating and the danger of anoxia increases with time So I cooled it as rapidly as possible by covering it with crushed ice and icy water

Tremont Smith You wanted to get the temperature down quickly only because of the sensitivity of the brain to anoxia?

Andjus I am not sure it is the brain Perhaps it is the heart

Dugal Did you make any blood studies studies of blood sugars for instance?

Andjus Yes After 2 hours in the jar and when the body temperature of the animal is about 15°C there is a tremendous hyperglycemia a 100 per cent increase There is also a significant increase of the concentration of inorganic phosphorus in the blood On the other hand there are no significant changes in the concentration of nonprotein nitrogen

Burton I dont suppose you did any studies in magnesium did you?

Andjus No I did not During and after rewarming the following changes result If the animal was cooled not lower than 15 C and then rewarmed during rewarming the blood sugar concentration regains its normal level If however the animal was cooled to 0 and then rewarmed to normal body temperature especially in rats that die of a secondary delayed death hyperglycemia is present in the beginning and then during the first 7 to 10 hours the blood sugar concentration falls below the normal level reaching sometimes very low values If the secondary death occurs 1 or 2 hours after rewarming the animal dies with hyperglycemia if it dies 10 hours later it dies with hypoglycemia (3)

Fremont Smith But not in convulsions?

Andjus No generally not in convulsions Occasionally however I have seen convulsive seizures in these animals but I do not know whether they were related to the blood sugar level or not

Hedblom Dr Andjus in case I am unfortunate enough on my Antarctic expedition to lose a sailor over the side into the Ross Sea and fortunate enough to get him back before a killer whale or a leopard seal gets him and I have a diathermy would you recommend that I apply the diathermy over the upper thorax mid thorax over the liver or where in order to give the greatest degree of efficiency? I do not expect he is going to get this cold but I contemplate using diathermy

Andjus Be careful because you can burn with diathermy It is difficult to warm a large part of the body quickly enough with diathermy We experienced trouble with our monkeys It is much easier to heat locally It would be quite enough to heat just the cardiac area as rapidly as possible

Smith It is necessary to find out whether the mans heart is beating *I do not think that there is any point at all in heating the* heart when it is already beating You do not want to beat a horse which is already going

Andjus That is right

EDITOR'S NOTE Dr Andjus would like to add the following "after-thought" to his remarks at the conference.

> Although our method of applying heat locally to the chest
> was devised f
> heart, and alt
> for the recov
> heart action,
> (1) local application of heat to the chest, which is easier to achieve is all that is necessary in order to rewarm the patient and (2) that preferential heating of the chest could be advantageous over generalized heating in cases of deep hyperthermia with a greatly depressed heart action Our current experiments on dogs speak in favor of such a possibility

Smith The local heating of the heart, at any rate, would be useful only if it was stopped Also, as far as Dr Lovelock and I can tell, better results can be obtained with general heating of the whole body because every time the heart sends out a certain volume of blood to the periphery it gets back cold blood in exchange We have convinced ourselves that although Dr Andjus's method worked very well, we can really obtain better results with general heating of the whole body

Fremont-Smith Once the heart is heated, or anyway?

Smith Anyway

Andjus But you are using small animals, Dr Smith, and it is relatively easy to warm rapidly a small body with diathermy without getting burns, but it is very difficult to warm a large body with diathermy without getting peripheral burns and burns in the extremities

Smith Dr Lovelock feels that the frozen parts must be thawed as quickly as possible So, if a sailor has a frozen foot or a frozen hand, Lovelock would advise thawing it as rapidly as possible After that it is not necessary to go on heating Thaw it quickly, get rid of the ice, and do not have it thaw gradually All of Dr Fuhrman's work supports that idea and much other work on isolated tissues and organs does, also

Lewis There is another complication that comes if the whole body is rewarmed before the heart starts beating In our experiments with dogs and rats cooling to these low temperatures we had some neurological damage if we rewarmed the entire body, for apparently the nervous tissue got to a temperature where it demanded oxygen before it got enough blood from the heart But when we just rewarmed the chest, until the heart started beating using hot water we did not have nervous tissue damage

Smith I find Dr Lewis's experiments particularly interesting Since Dr Andjus left we have tried reviving rats and hamsters by immersing them in hot water It was perfectly true that they could be revived but they tended to get convulsions if they were immersed in hot water That is possibly just what Dr Lewis has mentioned that we were heating the nervous tissue too quickly the same as when diathermy is used for rewarming and the re warming continues too long convulsions can result

Diathermy should be used rather carefully the animal should not be cooked or overheated it should not be burned or heated too long

Andjus May I ask you how to do it? When I was at Mill Hill these experiments with the monkey showed that it was very difficult Heating the whole body rapidly represents many technical difficulties

Smith The diathermy apparatus used was an experimental model Perkins is busy now building a new one It is a matter of getting the right kind of diathermy Perkins has done a lot of research since you left

Fremont Smith Dr Smith one thing that seems a little contradictory is that you said on the one hand you got better results with general warming whether or not the heart was beating and on the other hand you said it was not good to get the brain warmed up too soon if the heart was not beating How do you avoid getting the brain warmed up with general warming when the heart is not beating?

Smith First of all I would like to say by comparison with the rat the golden hamster was relatively easy to resuscitate after respiratory and cardiac arrest a situation that never occurs in natural hibernation The animals were not hibernating many of these experiments were done in midsummer The animals were relatively easy to resuscitate from body temperatures above 0 degrees If treated just like the rat they could be kept with arrested heartbeat and arrested breathing in ice for at least 4 hours and the possibility of reviving them was almost certain It was not necessary to heat the heart locally The animals could be revived at room temperature which in England is 20 C not perhaps the temperature you have here The 68 F you mentioned Dr Simeone is a nice cozy warm temperature with us

These hamsters with cardiac and respiratory arrest at body temperatures above 0 degrees could be resuscitated by artificial res

piration alone Sometimes animals were given artificial respiration under a bench lamp This enabled us to resuscitate them a bit more quickly These were unfrozen hamsters

Some animals kept in ice for 7 hours were resuscitated by these simple means but results were better when I warmed the body with diathermy not very quickly but by raising the colonic temperature by 1 degree a minute

With frozen animals I again tried heating the heart locally but found that if the animals had been freezing for 15 minutes or more they could not be resuscitated The heart would stop beating while the periphery was still frozen stiff and these animals did not recover So I consulted Dr Lovelock who said what I needed was to rewarm them with diathermy and get them thawed quickly

The first object was to thaw them quickly and then to rewarm them more gradually I worked out a standard method for warming the frozen or supercooled animals and also those which had been kept a long time in ice with body temperatures above 0 degrees I rewarmed them quite gradually approximately a degree or two a minute with diathermy

Fuhrman The whole animal?

Smith The whole animal yes so that when the heart started beating instead of getting back ice cold blood from the periphery and being thereby inhibited it went on beating more and more quickly so that the frozen or supercooled animal recovered rapidly (11)

Time passed and one day the diathermy apparatus broke down just as I was going to start resuscitating a hamster which had been freezing for about 50 minutes or so I did not want to lose the animal so I carried on giving it artificial respiration under the gentle warmth of a 60 watt bench lamp This hamster recovered completely

Then in co-operation with Dr Goldzveig (12) from Santiago Chile we tried to determine whether or not ice cold rats and ice cold mice with arrested heart and breathing could also be resuscitated very simply without microwave diathermy or complicated apparatus and we found that mice and even rats could be very readily resuscitated by giving artificial respiration and applying gentle warmth to the whole surface of the body

On the other hand if they were immersed in hot water probably the heart would beat and then in due course the animals would have convulsions When we warmed hamsters with diathermy and

then plunged them into hot water just when they were starting to breathe again they often had convulsions and died which suggested that it was possible to overdo the heating of the body even when the temperature had risen to from 15° to 20 C (13)

Lewis Does that mean hot water is a more efficient method of warming than diathermy?

Smith No I think that is why no one had revived ice cold animals before I have been very puzzled and I think Dr Andjus must have been too as to why it was that it was left to us to do these experiments why no one had resuscitated very cold animals earlier

Andjus I succeeded in reanimating a few rats just by putting them in hot water and giving artificial respiration

Smith They tend to have convulsions particularly if the water is rather hot

Tremont Smith Your question was whether it was more efficient in terms of getting body temperature up?

Lewis Yes getting it up quickly

Tremont Smith But it may be less efficient in terms of survival Do you think this is brain sensitivity?

Smith I really would not like to theorize but the way they had convulsions suggested to me that it might well be the brain which was upset

Burton May I supply a technical detail here which I hope may be of some use to people who are working on this It happens I got my Ph D degree on a thesis (14 15 16) about heating by high frequency waves and why different tissues become hotter than others It turned out to be just classical physics There is a law by which by changing the frequency (or wave length) one can select the kind of tissue which will be heated more than other kinds Others (17) in Germany who published on the same subject a year later reached the same conclusion

The law is in absolute units

$$\lambda \quad \frac{nK}{2}$$

λ is the specific conductivity of the material which will be selectively heated λ the frequency of the electromagnetic field and K the dielectric content (about 80 for most tissues) In practical units this becomes

λ = [illegible] x 10 [illegible] ohm [illegible] where λ = wave length in meters

or λ = 4 9 λ x 10 [illegible] ohm [illegible] where λ [illegible] frequency in mc

With short waves, the selective effect is quite marked, and tissues whose electrical properties do not satisfy the above equations are heated much less than those that do Since the specific heats differ for different tissues, the distribution of the rise of temperature produced by different frequencies of reduction can be a very complicated matter of prediction

By choice of the proper wave length of diathermy, it seems to me one could do quite a bit in heating the blood selectively, so that brain cells are not heated as much as the blood which is coming to the brain It might be very worth-while to look into the matter of choosing the wave lengths

Smith There is research along these lines going on quite actively at Mill Hill Perkins has your paper

Horvath Dr Smith, this use of the term *diathermy* is just a vague and rather unsatisfactory term Diathermy, in the common use of the term, applies to the longer wave lengths and not to the shorter ones which are now being employed When you talk about diathermy in these experiments, are you talking about the second?

Smith Mine is conventional diathermy

Horvath Do you mean 100 000? It makes a great deal of difference

Burton Again, there is a vast difference in the way you heat, whether you use electrostatic field, a condenser field, or whether you use electromagnetic heating, so called

Smith The small diathermy apparatus which I used consisted of an oscillator operating at a frequency of 27 mc per sec, with an output power of 120 watts, approximately

Burton That is a condenser field

Smith A condenser field

Burton Bigelow (18) for many years has been reviving monkeys by using the electromagnetic coil

Smith We tried a coil and liked this better

Horvath There is a very interesting thing which has been ignored When you used the magnetron with a 10 cm wave length the brain tissue of these small animals may also have been involved

Smith The rat brain did not get in the field It was shielded out

Horvath But the spinal cord was in the field and it is very selectively heated by 10 cm wave lengths It is also true, as Dr

Burton has pointed out, that there are differences. I read that work a number of years ago. Since that time there has been more work on shorter and different wave lengths in the centimeter area and they have been shown to be very specific for different types of tissues. In fact it is a technique now used for measuring various kinds of protein.

Smith: I am more interested in animals than in waves.

Horvath: This I think brings up a real point though: what is it that you are heating when you apply these methods of heating? What do you heat first: the skin, the subcutaneous tissue, the muscle, the heart, the blood or the brain or other nervous tissue? Do the responses of these organisms seem different with the procedure of heating?

Smith: The hamsters did not get convulsions when heated with diathermy. It was when I dropped them in hot water that they developed convulsions or if I heated them too rapidly or if I continued heating with diathermy until the deep body temperature in the colon reached 25° to 37° C.

Horvath: The diathermy could raise the tissue of the central nervous system to 45° or even 47° C, which would induce convulsions.

Smith: As you saw in the picture, the upper electrode of the diathermy was not over the whole head; it finished about at the level of the ears so that the brain may not have been heated. When I was using the diathermy by the method shown, heating was discontinued when the deep body temperature reached +10° C.

Fremont-Smith: Would the spinal cord's heating cause convulsions?

Horvath: The same thing might occur.

Smith: By the method used it did not. The convulsions occurred after immersion in hot water.

Horvath: Except when the rectal temperature of the rat was a little bit higher.

Smith: If you went on overheating the animal it would have convulsions.

Horvath: That is right, because that is when you raise the temperature of the brain in this area of forty-odd degrees C, where convulsions are ordinarily induced.

Fremont-Smith: The spinal cord you mean?

Horvath With some of the other devices that are specifically absorbed in the brain tissue there might be an increment in temperature of that tissue to such an extent that tremendous activity would be excited there and convulsions induced This might be done by other means besides this

Burton Actually Dr Stafford L Warren Dean of the Medical School University of California at Los Angeles and co workers in Rochester* did a lot of work with diathermy of calves (they wanted a big animal) with different wave lengths showing how different the temperatures produced by different methods were This point is very important for those who are going to use diathermy They should be made aware of these variations in different kinds of heating and should pay more attention to the proper choice of wave length

Andjus May I give you some more information about the magnetron? First of all I would like to stress the fact that we obtained with that kind of heating a revival of 100 per cent of the refrigerated and inanimate rats so I would not say that we damaged the brain tissue by this method This was a 500 watt magnetron operating at a frequency of 3000 mc per sec Figure 99 illustrates the distribution of microwave energy

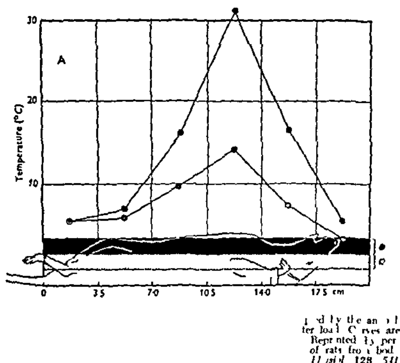
Lewis Is that short wave diathermy?

Andjus No it is microwave diathermy (4)

Horvath This is microwave diathermy and there is a great difference between microwave short wave and so called long wave which was the old conventional diathermy also they heat in very different ways The old conventional diathermy used to heat primarily on the surface the short wave diathermy heated primarily just a little below the surface and so called microwave was supposed to heat primarily underneath the surface This does not mean however that they do not heat the areas in between or below All areas are heated to some extent and the transfer of the heat may be by conduction by radiation and other means Some of these areas are heated more specifically than others and therefore in discussing the various ways in which an animal is revived we must know specifically what the temperature of any part of this organism is

Smith Dr Horvath we are not ready to tell you all these things We are leaving it to you people to do some more work

*Personal communication



p d by the an l ter load C rves are Repr nted by per of rats fro bod *H ysiol* 128 511

1955

Andjus Figure 99 shows the distribution of microwave energy in the area occupied by the animal The estimation was made by measuring the heating effect on water loads It is evident that the peak of the temperature curves is situated over the heart area

Figures 100 and 101 give further information about the rise of body temperatures during heating by microwaves Temperatures were taken *in the colon and in the esophagus not in the heart* The rise in temperature was recorded in an animal during actual reanimation as well as in the corpse of an animal that did not revive during heating When the temperature curves are compared the difference between the corpse and the reviving animal is evident as well as the difference between the temperature taken in the *esophagus beneath the heart and in the colon*

Horvath Were these temperature measurements made while the unit was on?

Andjus Yes it was on

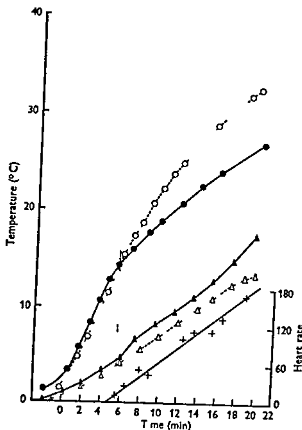


FIGURE 100 R se in temperature l nα e m L

a u s ● d O esophageal ten peratures x—x l art rate
Rep nted by permis on from And us R K and Lovelock J E Rean n at on of r ts from body ten peratures bet veen 0 and 1 C by m crow ve d therm y J Pl js ol **128** 541 (1955)

Fremont Smith Was the actual temperature read while the machine was running or did you stop the machine to read the thermometer?

Andjus No I did not stop the machine

Horvath Then your temperatures I must confess must be somewhat in error They are too high Their values are higher than they actually are

Andjus That is right

… under the cond… stopping the machine during ten… I get much the same results

Travell The comparative results still remained?

Andjus Yes The figures show that the difference between the corpse and the reviving animal, as far as the rise in temperature is concerned, starts with the first heart beats in the latter

Lewis I would like to make a comment about the convulsion which occurred with surface rewarming using hot water We have used surface rewarming with hot water almost exclusively to resuscitate rats cooled to these temperatures and we have had no convulsions but there is one difference in method We apply the water only to the chest to begin with

It is possible that some other mechanism rather than the overheated brain could explain the convulsions Alkalosis, for example, could produce them We have always used 5 per cent carbon dioxide in oxygen with artificial respiration during resuscitation

Hedblom What did you use for artificial respiration?

Smith Just air

Kark What was the time of these convulsions?

Andjus During the rewarming period If the animal dies during rewarming it dies always with hyperglycemia

Smith Figure 102 shows the typical cooling curve of a hamster immersed in a bath at –5° to –8°C It supercooled until the colonic temperature reached just below –5°C, and then although the animal was still immersed in the sub zero bath, the colonic temperature suddenly rose to –4 56°C and spontaneous crystallization began The ears began to stiffen the skin hardened and then I started to rewarm it

Figure 103 shows another typical cooling curve from an animal which became supercooled and was rewarmed without evidence of ice formation anywhere in the body It was like the animal previously mentioned Figure 104 shows the typical cooling curve of a hamster which froze progressively The colonic temperature fell to a level just below 0 degrees and then dropped very little over the course of the next hour during which time the animal became progressively harder and there seemed little doubt that it was in fact freezing



FIGURE 101 Comparison between a reviving rat and a reviving monkey. The vertical line marks the onset of circulation. At the beginning of heating the temperature of the monkey ranged from a peripheral temperature of 0° to a central temperature of 5.8°C. The temperature of the rat was 0.3°C throughout the body

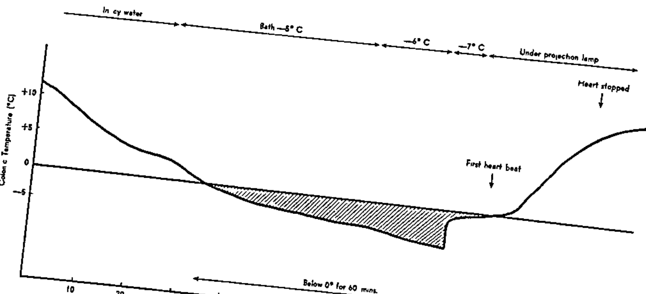


FIGURE 102 The colonic temperature of a hamster which became supercooled to −5.75°C and then crystallized spontaneously while still immersed in the sub zero bath Reprinted by permission from Smith A U Lovelock J E and Parkes A S Resuscitation of hamsters after supercooling or partial crystallization at body temperatures below 0°C *Nature* 173, 1136 (1954)

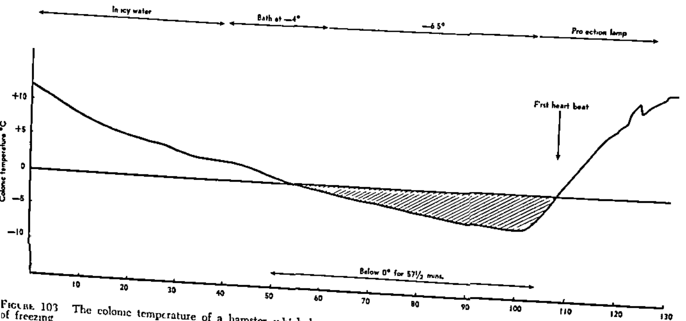


FIGURE 103 The colonic temperature of a hamster which became supercooled to −5°C and was rewarmed without evidence of freezing

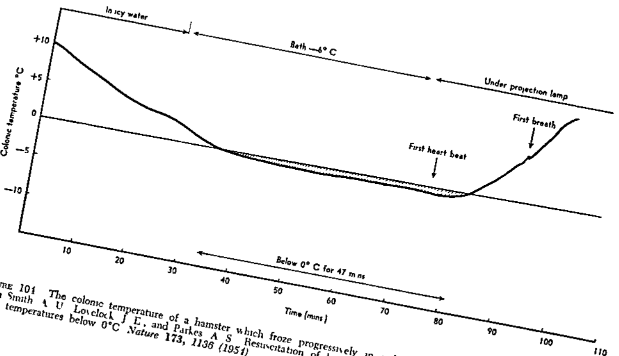


FIGURE 101 The colonic temperature of a hamster which froze progressively in a bath at −6°C Reprinted, by permission, from Smith A U Lovelock J E, and Parkes A S Resuscitation of hamsters after supercooling or partial crystallization at body temperatures below 0°C *Nature* **173**, *1136 (1954)*

People have asked me how we knew that ice was formed in these animals One method was very simple Capillary tubes containing Ringer s solution were inserted into the subcutaneous tissue or into the peritoneal cavity When removed lumps of tissue were often pulled away too and there were ice crystals sticking in them If on the other hand the tubes were lubricated with vaseline or with glycerol it was easy to remove them and show that they contained ice crystals

The other method was conclusive We transected a number of hamsters *some of which were dead and at room temperature there* were others which were apparently lifeless and had been freezing progressively or which had supercooled It was instructive to transect animals which had been freezing for various periods of time *When they had been freezing for about 40 minutes the skin* and the musculature were hard stiff and crystalline The skin of *the hamster is so loosely attached to the underlying tissues that in* animals transected at room temperature it falls away from the body wall *After freezing for 40 minutes however the skin* was firmly attached to the body wall and when the animal was cut in half the surfaces were absolutely flat (19)

Inside the peritoneal cavity there were ice crystals between the various viscera Pieces of ice shaped according *to the organ that* they had been up against could be withdrawn No special apparatus was required to watch them thaw out at room temperature and they definitely were ice crystals

There was no doubt about the fact that there was ice *not only* between the various organs in the peritoneal cavity but within the bladder and the stomach The cut surfaces of the liver and the kidneys were also crystalline in consistency

Having convinced ourselves that these animals really *were frozen* we then began to wonder what proportion of the body water had been converted to ice in animals which were subsequently resuscitated and whether in those animals which I had failed to resuscitate there was present more than a critical amount *of ice*

In one series of experiments animals were frozen for *different* lengths of time These were all resuscitated by the same method diathermy Table XII shows that in animals frozen for from 50 to 70 minutes there was beginning to be a mortality *Of the twenty* hamsters which were frozen at −5 C for periods varying from 50 to 70 minutes seventeen recovered fully that is recovered heartbeat consciousness reflexes and spontaneous activity I t

TABLE XII

The Relation Between Duration of Freezing and Degree of Recovery

Duration of Freezing with Colon Below 0 C (min)	Number of Hamsters	Results of Resuscitation (death or survival + A R) +	++	+++	++++	Number of Long Term Survivors
30 to 39	16				16	16
40 to 49	24				24	19
50 to 70	20			3	17	8
90 to 120	3		1	1	1	0
120 to 159	3		2	1		0
160 to 170	4	3	1			0
174 to 180	3					0

+ Heart beat only
++ Heart beat and breathing
+++ Posture and consciousness
++++ Complete recovery died within 24 hrs

nine of those seventeen died within from 24 to 48 hours and there were only eight long term survivors

Among those frozen for 90 to 120 minutes only one recovered completely and it died overnight After from 60 to 70 minutes freezing we were getting to a limit The animals had been frozen to an extent which with the methods of resuscitation that I was using was not usually compatible with long term survival

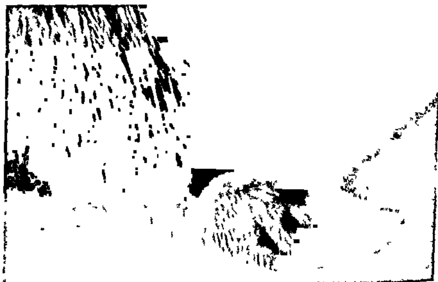
Lewis How long had the heart stopped in these various groups?

Smith The heart stops when the body temperature is about +2 C somewhere between +1 and +3°C and there would be another 10 or 15 minutes before freezing started so an animal which had been freezing progressively for 70 minutes by the time rewarming was started had already been 85 minutes without heart beat and breathing

But in the golden hamster kept on ice with a body temperature just above 0 as I mentioned a period of 4 hours of arrested heart beat was compatible with full revival and complete recovery providing there had not been the complication of ice formation So



FIGURE 103 Normal hind paw of hamster (x2) Reprinted by permission from Smith A U Frostbite in golden hamsters revived from body temperatures below 0°C *Lancet* 2, 1255 (1954)



(x2)
evived

his was not just that we had reached the time limit for keeping hem without heartbeat This was something else We thought must be the amount of ice and that there was a limit to the xtent to which hamsters would stand having their body water emoved in the form of ice We were trying to find out what the mits were

Figure 105 shows a normal hind paw and Figure 106 the hind aw of a hamster showing frostbite The paw shown in Figure 106 was bent when it was in the frozen state at about the level of the netatarsophalangeal joint and when rewarmed it became hyperemic mmediately and swelled up within a few hours

Figure 107 shows one of the toes I was delighted earlier in the liscussion when Dr Kulka described practically everything that

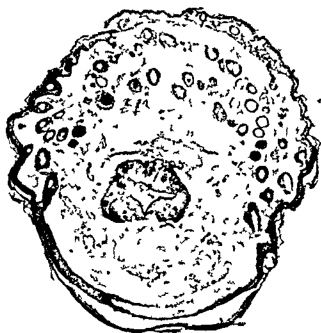


FIGURE 10 Transverse section through the middle phalanx of toe 3 days after bending the frozen metatarsophalangeal joint (x50)

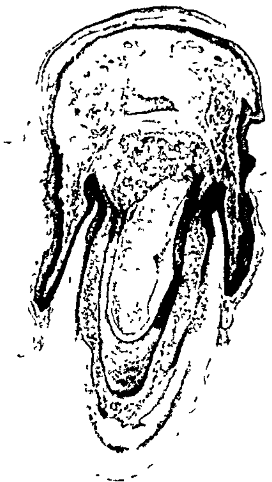
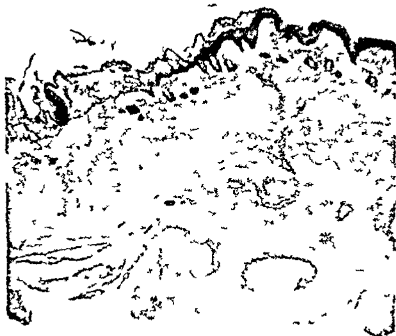


FIGURE 108. Longitudinal section through distal phalanx of toe 3 days after bending the frozen metatarsophalangeal joint (x50). Reprinted by permission from Smith, A. U. Frostbite in golden hamsters revived from body temperatures below 0°C. *Lancet 2*, 1255 (1954).

I had seen focal lesions in blood vessels and the fact that there could be as can be seen here blistering on the surface and degeneration of the epithelium and yet hair follicles that were normal Bad changes in the nail bed were shown in a longitudinal section through the toe (Figure 108)

The skin of the dorsum of the paw also showed blistering on the surface and edema (Figure 109) 24 hours after it had been bent in the frozen state There was a great infiltration with polymorpholeukocytes mononuclear cells and plasma cells The underlying tendons underwent very severe degeneration

Figure 110 shows the early changes in a pinna 24 hours after it had frozen stiff The tip was beginning to harden and undergo



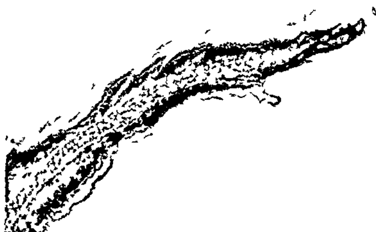


FIGURE 110 Section through the tip of the pinna 24 hours after bending the frozen part halfway along its length (x75)





FIGURE 113 Section through the left pinna 7 days after it had been frozen stiff but not bent in the frozen state (x10)

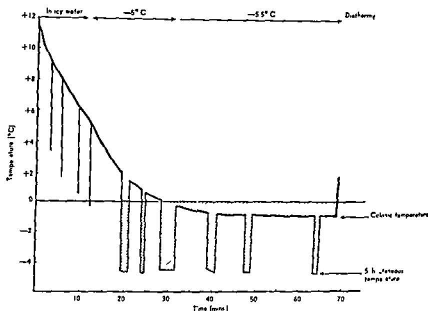


FIGURE 114 The colonic and subcutaneous temperatures recorded from a hamster which froze progressively while immersed in a bath at −5 5°C

Smith I will describe that later.

Andjus I asked you that because in my experiments I invariably get a spontaneous rise of the subcutaneous temperature when freezing starts after supercooling

Smith You do sometimes, but not in this particular one The proportion of water which had been converted to ice in the skin

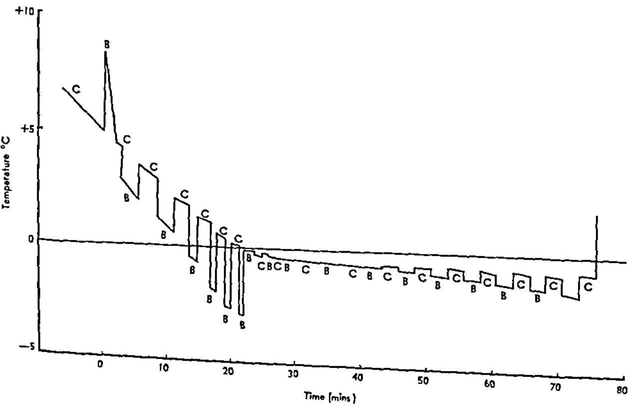
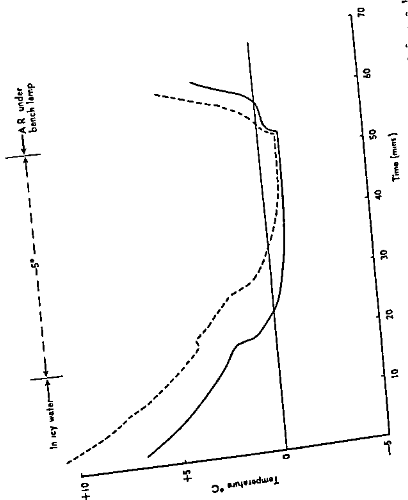


Figure 115 The cerebral and colonic temperatures recorded from a hamster which froze progressively while immersed in a bath at −5°C

C = colonic temperature
B = cerebral temperature



hamster which froze

Smith: I passed the thermocouple a sufficient distance to lie at the lower end of the thoracic esophagus, so it was adjacent to the heart.

Fremont-Smith: In the esophagus?

Smith: Yes. I passed it down the esophagus.

Fremont-Smith: Then it is really esophageal temperature rather than intrathoracic.

Smith: But it is intrathoracic. The esophagus is in the thorax. I did not want to make too many holes in these animals because I wanted to revive them and not to give them too much disability during their period of convalescence.

We did a lot of work. Lovelock was away but it was his method and I did the arithmetic. Somebody checked it for me. Table XIII shows the proportion of water converted to ice in different regions of hamsters frozen for from 40 to 60 minutes. There was a certain amount of variation in different animals: some were fat and some were thin. It was not possible to be sure of freezing for the same length of time or always to be sure of putting thermocouples in exactly the same place in the subcutaneous tissue. After 40 minutes somewhere around 60 per cent of the subcutaneous fluid was frozen; at the end of 60 minutes, generally around 90 per cent. This was quite a small group of animals but the amount of water frozen in the thoracic esophagus was decidedly lower than in the other regions including the colon.

I still wanted to know what proportion of the total body water had been converted to ice and so Dr. Lovelock suggested our

TABLE XIII

The Proportion of Water Converted to Ice in Different Regions of Hamsters Frozen Progressively for from 40 to 60 minutes at −5°C

Region	Water Frozen (per cent)
Subcutaneous tissues	59 to 89
Brain	53 to 62
Thoracic esophagus	7 to 22

doing some calorimetry this was quite simple We dropped animals which had been frozen for varying periods into a simple calorimeter containing a known volume of water at a known temperature and then recorded the fall in temperature of the water in the calorimeter and the rise in the deep body temperature of the animal We then went on until equilibrium was reached and then it was quite easy knowing the weight of the animal and so forth to determine how much of the fall in the temperature of the water of the calorimeter was caused by melting ice All this will be published so I need not go into it in very great detail but we checked on the calorimetry very carefully and although it was a simple method we did seem to get an accurate determination of the amount of water frozen

One way that I checked on the calorimetry amused my colleagues a great deal I made artificial hamsters from polythene bags of suitable hamster size stuffed them with cotton wool put in known volumes of distilled water and froze those Later I got ambitious covered the bags with hamster skin and stitched it up the bags looked just like hamsters I continued until I knew that all the water was frozen and then I estimated the amount of ice by calorimetry When an artificial hamster containing 50 ml of completely frozen water was dropped into the calorimeter the estimated amount of ice was generally somewhere between 49 and 51 grams of ice It seemed to me that that was good enough and that the calorimetry was accurate

Figure 117 shows results of animal experiments The percentage of water frozen determined by calorimetry is plotted on the vertical scale and the length of time for which the animals had been frozen with a colonic temperature below 0 degrees is plotted horizontally This shows that when the animals had been freezing for 40 minutes 15 per cent of the body water might have been converted to ice

At first there was rather a gradual formation of ice then the amount of ice formed increased rather sharply so that by 60 minutes anything from 30 to 40 per cent of the body water might have been frozen

After 80 minutes of freezing between 50 and 60 per cent of the water was frozen The exact amount varied with different animals After 3 hours of freezing between 70 and 95 per cent of the body water was frozen

We compared these figures with the results of resuscitation We had resuscitated 100 per cent of the animals which had been freez

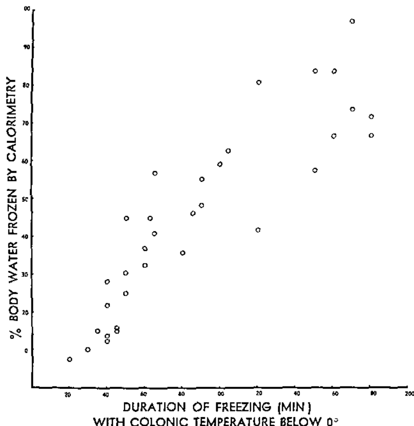


FIGURE 117 Calorimetric determinations of the proportion of body water frozen in hamsters which froze progressively for different periods in baths at −5 C

ing for less than 50 minutes so we felt that among the hamsters used for calorimetry it should have been possible also to revive those frozen for less than 50 minutes This group included animals in which 3 per cent or less of the body water had been frozen

Among animals frozen for more than 50 minutes there was a mortality, there was 50 per cent mortality in the group frozen for between 50 and 70 minutes That is the group where between 30 and 55 per cent of the body water was frozen

In the group frozen for between 80 and 120 minutes the animals would recover partially They might not even recover consciousness

Fremont Smith What was the maximum body water?

Smith We thought that somewhere between 30 and 40 per cent of body water frozen was compatible with reviving a high proportion of the animals We still could revive some animals when as much as 50 per cent of the body water was frozen

Burton Did you check your method by Lovelock s formula against this in particular animals?

Smith Yes

Burton And they agree?

Smith Yes remarkably well In all of the animals used for calorimetry and there were about 50 I also worked out by Lovelock s formula the proportion of the water which had become frozen in the colon using the final temperature recorded from the colonic thermocouple I was struck (and so was Lovelock) by the remarkable similarity between the proportion of water frozen in the colon and the proportion of water frozen in the whole body There was very seldom more than 5 per cent difference Generally the proportion of water frozen in the colon was about 5 per cent lower than the proportion of water which had been frozen in the whole body That difference was of course explained by the fact that the ice fronts reached the thorax and deep abdominal organs later than the superficial tissues As a result there was less ice formed either in the thorax or in the colon than in the superficial tissues For this reason calculations based on the minimum colonic temperature gave a low estimate of the total amount of body water frozen

I then went back and calculated and from the final colonic temperatures reached the percentage of water frozen in the colons of all the hamsters bearing in mind that these figures are likely to be between 5 and 10 per cent lower than the amount which had been frozen in the body as a whole We then tried to see what the relation was between the amount of body water frozen and survival

Among animals frozen up to 50 minutes there were hardly any casualties at all and the maximum amount of colonic water frozen was 45 per cent No animal in which more than 45 per cent of the water in the colon had been frozen recovered There might have been 5 or 10 per cent more total body water frozen but I think we can say that by the methods I am now using I would not be able to resuscitate an animal in which more than 55 per cent of the total body water was frozen

I do not think that this means that no one is ever going to do it because we still must look into the possibility of treating the animals with glycerol It will be necessary to introduce into the circulation a sufficiently high concentration of glycerol to protect the tissues from the otherwise damaging effects of the high salt concentration that occurs when the water is removed as ice

I might just mention a little about the post mortem findings There were some casualties I found the post mortem findings were interesting The chief cause of death when the animals were not resuscitated was massive hemorrhage into the stomach Of the animals that revived there were six that died from 7 to 10 days after they had apparently been completely resuscitated At autopsy they had perforated gastric ulcers A part of the stomach wall had been infarcted Some of them of course had general peritonitis and others had rather a bad condition locally round the hole in the stomach

I found it interesting that gastric hemorrhage was the common cause of death in animals which died either in a few hours or a couple of days after having been frozen and resuscitated We thought about this a good deal and this is one of the many problems we still have to investigate Dr Lovelock and I wondered whether some cause such as differential effect of cooling on enzyme action might be responsible for this We thought perhaps it might be tryptic digestion after the animal was so cold that there was no circulation in the stomach We have various other theories but no proof for any of them

One or two other lesions were rather interesting Just a few animals developed lens opacities and these reminded Dr Parkes most forcibly of the pictures in Professor Selye's report on stress (20) But there are other possible explanations of the changes in the lens some biophysical ones along the lines of altered permeability of the cornea and of the lens itself when temperature is reduced and I refer here to the work of Dr Davson (21 22) at University College

Andjus Do you find it after rewarming or before?

Smith I was speaking of changes which appeared after rewarming Hamsters rewarmed by immersion in warm water will develop corneal and lens opacities straightaway In frozen animals rewarmed by diathermy the lens opacities developed rather gradually over the course of days weeks or months after resuscitation which is rather what has been described after stress conditions

The gastric hemorrhages reminded us of the Curling's ulcers which occur sometimes in severely burned patients and which may also result from stress

Burton Have you thought whether or not this ulceration could be related to the ulceration of the intestines and stomach in shock? Dr Jacob Fine of the Department of Surgery at the Harvard Medical School is an enthusiast on this point that if the blood flow is stopped ulceration results

Smith Yes

Burton I wondered if you had tried penicillin in these animals

Smith No we have not I think it must be related with that work I am sure it is related in some way to the arrest of the blood supply into the part and we hope we will some day have time to look into it

Our very latest work is on the effects of freezing on the pregnant hamsters Dr Parkes main interest is in reproductive physiology and he was curious to know what the effects would be on fetal development of arresting the blood supply and the circulation and of cooling to different temperatures

The hamster is a remarkable animal in many ways and its reproductive cycle is particularly remarkable Pregnancy lasts only 16 days in the hamster and so the female does not waste any time Pregnancy is much shorter than in the rat the mouse or any of the other laboratory rodents

In the first series of experiments that I did animals at different stages of pregnancy were cooled to body temperatures below 0° Some of them supercooled and some of them froze They were kept at body temperatures below 0 degrees for from 30 to 35 minutes in a bath at −5°C

I revived the first group and let them go to term all the animals between the first and the thirteenth day of pregnancy recovered completely but those which were 14 or 15 days pregnant had premature deliveries were very sick and did not usually survive or if they did survive they did not have litters

Most of the other animals had litters but some showed annoyance at being examined daily which was our practice after resuscitation and although we avoided counting or handling the young and although some of them reared litters others tended to eat them So I did a second series of experiments in which I cooled hamsters which were 1 to 12 days pregnant and killed them all on the

thirteenth day of pregnancy in order to examine and count the fetuses I did not let the second lot go to term I had got young from the first lot, but I did not know how many and what the proportion was of fetuses to young reared

In the second series, the hamsters which were from 2 to 8 days pregnant at the time of freezing, and which were killed on the thirteenth day, had a full complement of normal fetuses, as shown in Figure 118

The hamster can have as many as twelve young, but, in general, under our conditions our animals very seldom have more than nine or ten Normally, I nearly always find one empty placental sac or one placental sac with a partially resorbed fetus

The same results were obtained whether these animals had been frozen from 30 to 35 minutes on the second, third, fourth, fifth, sixth seventh, or eighth day of pregnancy Of the three animals which had been frozen on the ninth day of pregnancy, each had nine resorbing fetuses and only one normal fetus (Figure 119) Higher magnification would show that all the normal features of a 13-day hamster are there in the solitary fetus the eyes, the nose, the mouth and the state of the skin and, internally it looked quite normal too Although all the other fetuses were resorbed, each animal frozen on the ninth day of pregnancy had one normal fetus

In animals frozen on the tenth day of pregnancy and killed on the thirteenth day, the whole lot of fetuses were resorbing (Figure 120)

In the animals frozen from 30 to 35 minutes at −5°C on the eleventh day there were two, three, or four normal fetuses and from four to six resorbing ones Figure 121 shows two normal fetuses and one undersized one which showed no abnormalities except for size

In this series of experiments the animal which was frozen on the twelfth day had perfectly normal fetuses on the thirteenth day This seemed to me most striking and suggested that there was a critical stage in pregnancy when freezing had very disastrous results Freezing on the tenth day of pregnancy gave the maximum effect, and freezing on the ninth and eleventh days also caused rather severe damage

There was a critical stage in fetal development when arrest of maternal circulation or exposure to intense cold was harmful, at the moment I do not know which, I do not know whether it is an effect on the fetuses themselves or on the placenta



FIGURE 118 The uterine contents on the thirteenth day of pregnancy of a hamster which had been frozen progressively for 33 minutes on the seventh day of pregnancy



FIGURE 119 The uterine contents on the thirteenth day of pregnancy of a hamster which had been frozen progressively for 30 minutes on the ninth day of pregnancy

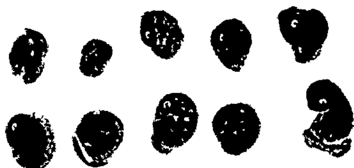


FIGURE 120 The uterine contents on the thirteenth day of pregnancy of a hamster which had been frozen progressively for 28 minutes on the tenth day of pregnancy



FIGURE 121 The uterine contents on the thirteenth day of pregnancy of a hamster which had become supercooled to a colonic temperature of −3°C and was below 0°C for 20 minutes on the eleventh day of pregnancy

Fremont Smith: But before or after was not so bad?

Smith: Before or after this critical period in pregnancy freezing from 30 to 35 minutes just did not seem to affect fetal development at all.

Then I started a third series of experiments and planned to freeze the animals just as long as possible compatible with resuscitating them. Straightaway I found that the pregnant hamsters would seldom survive freezing for 60 minutes. Freezing from about 49 to 50 minutes seemed to be the limit if the pregnant hamster was to be resuscitated, so I settled on freezing them from 45 to 49 minutes in a bath of −5°C, and I did just what I had done in the first experiment. I froze them on different days of pregnancy and then killed them on the thirteenth day to examine the fetuses. Again I found that in animals which were frozen on the ninth, tenth or eleventh day of pregnancy, this time from 45 to 50 minutes, there were very few normal fetuses in individual animals, confirming the belief that the period between the ninth and eleventh days is a critical stage in pregnancy.

I was more interested with the results of freezing animals which were from 2 to 7 days pregnant. In the previous series I had never seen any abnormal fetuses. In this series of experiments in which the mothers were frozen the maximum length of time compatible with revival I began to find fetal abnormalities. The fetuses were edematous. In some of them there was incomplete closure of the cranium so that the brain was up on the surface. There were large hemorrhagic patches on the fetuses too. And there were some resorbing fetuses. The fetuses from a hamster frozen for 45 minutes on the second day of pregnancy and killed on the thirteenth day are shown in Figure 122. I have not made any histologic studies of these so I cannot tell you what the abnormalities inside the animals are.

These results were very interesting and Dr. Parkes immediately saw that they tied in with work in other fields of embryology. There are certain toxic substances and radiations which can produce the same effects, that is to say, by treating the mother with certain noxious agents at critical stages in pregnancy abnormal fetal development will result. We shall have to follow this up a little. In this series when I was freezing the animals for the maximum length of time compatible with recovery, the one which was frozen for 49 minutes on the eighth day of pregnancy had a perfectly normal collection of fetuses, so it was not just the extra freezing



Figure 122. The uterine contents on the thirteenth day of pregnancy of a hamster which had been frozen progressively for 45 minutes on the second day of pregnancy.

It was a freezing at a special time in pregnancy which was the crucial part of this experiment. Freezing on the eighth or twelfth day had no effect on the fetuses at all.

Andjus: Do you have any evidence that these changes are related actually to freezing? Are those results basically different from the results obtained by Courrier and Marois (23) on the one hand and Vidovic (24)* on the other?

Smith: If Professor Courrier's (23,25) results are compared with mine they will be found to be the same sort of thing, only I have much greater effects. Anyway, he got no effects at all from cooling during the first week of pregnancy in the rat, whereas in the hamster cooling in the early stages, even day 2, when only from sixteen to twenty-four cells have formed, produced an effect.

Andjus: *I wanted to stress the fact that the quoted authors* cooled animals not lower than 15 C, and yet the same sort of abnormalities was found in the embryos and a similar differentiation between characteristic stages of pregnancy related to the effect of hypothermia was also described.

*Also unpublished data.

Smith It was not in the early part of the pregnancy they did not get results like this This is a species difference and also the fact that we are actually freezing the animals and working at a lower temperature range

Andjus How did you know it was a specific effect of freezing?

Smith Dr Andjus I had quite a lot of animals which were pregnant and not frozen I do not have time to give the figures but anyway the first series of experiments was a control on the subsequent ones

Andjus During my stay in your Institute I cooled some rats to zero for Dr C R Austin of the National Institute for Medical Research in London who examined the unfertilized eggs of the females after rewarming from zero He noticed some parthenogenetic development

Smith Yes

Andjus Is there anything new in that field?

Smith I think that Dr C R Austin had already found in Australia that by cooling the fallopian tubes by local cooling parthenogenetic development can be obtained in mammalian eggs Dr Austin has not published that work but I do not think cooling the whole animal had a much different effect from cooling the isolated segment of the fallopian tube

Andjus We found that there is definitely some parthenogenetic activation of the egg induced by cooling the whole body to zero This was noticed after rewarming the animals but it did not last long

Smith Parthenogenetic development in the rat so far as I know has not been completed I do not think anyone has succeeded in demonstrating complete development from a parthenogenetic egg

Behnke I would like to report some experiments made at the U S Naval Radiological Defense Laboratory conducted by Dr Ralph W Brauer* and his co workers Dr G F Leong and Mr R J Holloway who have employed the hypothermia induction method of Andjus and Smith (3 26) to produce hypothermia and surgical anesthesia in rats without the use of anesthetics other than carbon dioxide The rats were cooled so that their deep body temperatures were in the range of from 14° to 20 C The livers were then removed and perfused Such livers function normally for periods of from 6 to 8 hours Bile production in the in vitro

*Unpublished data

liver preparations kept at room temperature returned to normal following depressed function in the cooled animal I mention this as one of the functions of an isolated organ that recovers when removed from the hypothermic animal

EDITOR'S NOTE Dr Behnke would like to add the following communication received from Dr Ralph W Brauer of the U S Naval Radiological Defense Laboratory

> *For some time a fairly extensive series of studies concerning liver function in relation to temperatures in the subnormal range has been in progress at this laboratory* Bile flow and composition chromic phosphate colloid uptake sulfobromophthalein uptake *and excretion into bile* and hemodynamics have been investigated from this point of view in the isolated rat liver preparation results were briefly mentioned at the
>
> approach to problems in the field of liver physiology these studies in the isolated liver are now being paralleled as far as possible by studies *in vivo* in the intact animal Two techniques have been employed by us to date for this purpose The first has been the application by Dr G F Leong and Mr R J Holloway of the hypothermia induction methods of Andjus and Smith to produce hypothermia and surgical anesthesia in rats without use of anesthetics other than carbon dioxide such preparations were cooled to rectal temperatures of from 14° to 20 C and employed as liver donors for perfusion experiments Such experiments have shown that recovery of bile flow can be obtained on perfusion of livers cooled to temperatures of from 16° to 18°C *in vivo* Since livers equilibrated with blood in the perfusion apparatus and then cooled to comparable temperatures recover in less than 20 per cent of experiments the above observations suggest presence of a recovery factor either in fresh livers *in vivo* or in fresh whole blood and disappearance of this factor on continued perfusion

A second approach followed by Lieut Comdr G M Moore has consisted in threading a silver constantan thermocouple via a No 30 gage needle through the substance of the right lobe of the rat liver to determine liver temperature *in vivo* in relation to deep body temperatures and to various liver functions during cooling or rewarming of such preparations under light nembutal anesthesia

In general liver temperatures are slightly higher than rectal temperatures the difference being perhaps 1°C On cooling the animals at a rate of about 0 2 C min by means of ice packs rectal temperatures fall much more drastically than liver temperatures so that when rectal temperatures have reached 25°C the tempera

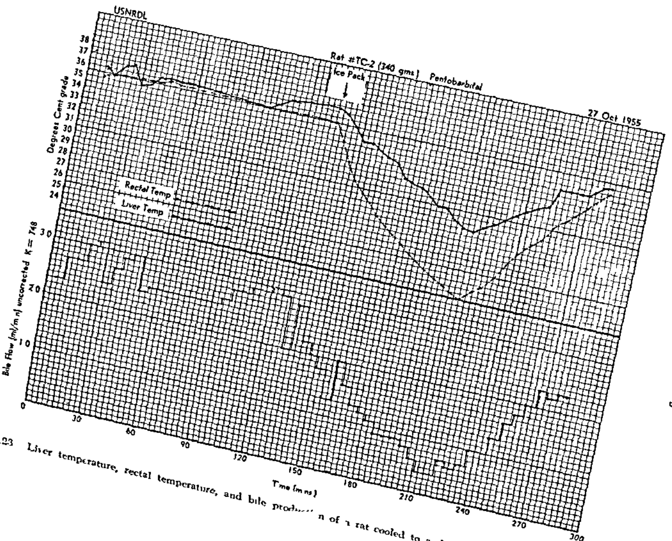


FIGURE 123 Liver temperature, rectal temperature, and bile produ... n of a rat cooled to a deep bod... ... ture of ~23°C

ture difference between liver and deep rectum may exceed 5°C. On rewarming, liver and rectal temperatures retrace their respective courses. Since the liver in the rat accounts for about 5 per cent of the body weight and receives a blood supply equivalent to about 65 per cent of the total circulating blood volume each minute, these values suggest that in the hypothermic rat the contribution of the liver toward temperature regulation may not be negligible.

Bile flow falls sharply with decreasing liver temperature: the relative rate of bile flow decrease with temperature averages about 80 per cent over the 10 degree range between 38° and 28°C, or a Q_{10} of 4 to 5. This value is close to that found for the isolated rat liver *in vivo*, and is much larger than the Q_{10} of 2.15 reported for the urethanized intact rat. The reason for this discrepancy is as yet unknown, although it may be related to a report that urethane reduces bile flow. Other aspects of liver function in this preparation are now being investigated.

Fremont-Smith: How many hours did these livers stay alive, from 6 to 8 hours?

Behnke: Outside the body normally, they live this long. In another series of experiments, thermocouples were put into the liver *in vivo*. I have one graph which shows the fall of temperature in the liver, in relation to bile production.

The upper graph of Figure 123 shows the liver temperature of a rat cooled to a deep body temperature of −23°C. The rectal temperature, the liver temperature and the bile production are shown. There is no hunting reaction here.

Fremont-Smith: How low did the liver temperature go?

Behnke: In this particular experiment the liver temperature was of the order of 30°C. It is considerably higher than the rectal temperature which went down to 23°C.

It is interesting that the techniques used by Dr. Smith and Dr. Andjus are being applied to an isolated organ preparation, and when you come to San Francisco, Dr. Smith, I think that you will be able to help the investigators with this type of work.

Smith: Captain Behnke, what Dr. Andjus and I did was really to suffocate the rats. Was Dr. Brauer just anesthetizing them in carbon dioxide only, or was there some anoxia? If there was anoxia, it is most important that that liver seemed so normal afterward.

Behnke I believe that he found that only carbon dioxide was necessary and that he administered oxygen to prevent the oxygen content of the air in the bottle from falling to a low level

Smith He mentioned that he had cooled them, that he had used carbon dioxide only without any anoxia, and I wondered whether that liver was one of the ones which suffered anoxia as well as hypercapnia

Behnke This is a critical point and I will ascertain the facts later, if I may

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BLOCKADE TECHNIQUES AS PROTECTIVE MEASURES AGAINST VENTRICULAR FIBRILLATION DURING HYPOTHERMIA

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SOME YEARS AGO experiments were carried out by Bigelow and his associates (1) in Toronto and Boerima and his colleagues (2) in Holland to find out whether the use of acutely induced hypothermia might permit one to interrupt safely the function of the heart for a period of time, with the ultimate objective of using this method in order to perform intracardiac surgery in a bloodless field A great deal of work has been done in an effort to understand the physiologic alterations that take place during acutely induced hypothermia and I shall not refer to this work since you are undoubtedly familiar with it A sizable clinical experience has also been achieved especially by Dr John Lewis of Minneapolis, who is here with us, and by Dr Henry Swan of Denver

All of us who have worked with venous inflow occlusion of the heart and cardiotomy under acutely induced general hypothermia are impressed with the fact that the principal hazard is ventricular fibrillation Ventricular fibrillation may occur in the hypothermic state without venous inflow occlusion or any cardiac manipulation It is much more apt to occur during vena caval occlusion and certain manipulative procedures It has proved to be less troublesome a problem when the right atrium or the pulmonary artery is opened during venous inflow occlusion than when the ventricle is opened Most workers have found that the performance of a right ventriculotomy during hypothermia almost always brings about ventricular fibrillation

In the spring of 1953 in Paris Lian and his group (3) began to study the effect of the injection of a local anesthetic agent in the region of the sino-auricular node during drug induced hypothermia or what is commonly called artificial hibernation A brief note describing their success in preventing ventricular fibrillation

Figure 104. Area of procaine infiltration. The light area represents the area of infiltration; the dotted area the approximate location of the sinoauricular node. Reprinted by permission from Rule, A. Shinnake, H. B. [illegible] k, [illegible] Bouin, R. D. Ventricular fibrillation in the hypothermic state. Venn. [illegible] S. gery 38: 847 (1955).

by this maneuver was published in 1954 in the Foreign Letters section of the Journal of the American Medical Association We heard of their initial experiences and in December 1953 a group of us spearheaded by one of my young associates Dr Angelo Riberi (4 10) of Torino Italy began some studies in dogs with procaine blockade of the right atrial superior vena caval junction

I would like to describe briefly some of our experiences Figure 124 shows the site of the injection The injection is made in the general area of the junction of the right atrium and the superior vena cava The injection is carried over the anterior aspect of the junction somewhat posteriorly and along the intra atrial groove In all of our experiments we persisted with the injection until we obtained slowing of the heart rate and electrocardiographic evidence of alteration of the P wave

Ferrer What kind of alteration?

Shumacker In 70 per cent of the animals the P waves disappeared while in 30 per cent it was reduced markedly in voltage (Figure 125) This was true both in normothermic and in hypothermic animals It was also true in both groups that a slowing of the pulse rate occurred as well as a modest drop in the blood pressure

Montgomery How did you chill the animals?

Shumacker Whenever the animals were cooled they were anesthetized with intravenously administered sodium pentothal intubated immediately and for the remainder of the experiment hyperventilated with 100 per cent oxygen using a mechanical insufflator which inflated the lungs with oxygen at a constant rate During the process of cooling the animals were given just enough ether to prevent shivering Afterward they were given oxygen alone Undoubtedly there will be some discussion later about whether pure oxygen or oxygen mixed with a small amount of carbon dioxide is preferable In our experience 100 per cent oxygen was used constantly

Lewis Did you measure the pHs?

Shumacker No As is shown in Table XII in normothermic animals the average pulse rate before the anesthetic blockade was 143 and afterward 91 The average blood pressure beforehand was 174 122 and 165 98 afterward In the hypothermic animals (these data are just from a sample of ten and the results were similar in a much larger group) the average change in pulse rate was from 67 to 40 and in blood pressure from 140 110 to 125 78

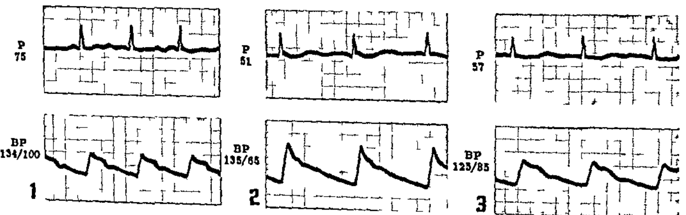


FIGURE 125 Effect of procaine injection of superior vena caval atrial junction upon electrocardiogram (lead 2) pulse and blood pressure in hypothermic dog temperature 27 degrees Reprinted by permission from Robert A Shumacker H B Jr Kajikuri H Grice P F and Boone R D Ventricular fibrillation in the hypothermic state V General discussion *Surgery* 38 84- (1955)

TABLE XIV*

Average Pulse, Blood Pressure, and Electrocardiographic Changes in Dogs With Procaine Block of Atrial-Superior Vena Caval Area

No of Dogs	Pulse Rate		Blood Pressure		Alteration in P Wave	Duration of P Wave Changes
	Before	After	Before	After		
			Normothermic Animals			
10	143	91	174/122 mm Hg	165/98 mm Hg	Disappeared 70% Altered 30%	9 7
			Hypothermic Animals			
10	67	40	146/110 mm Hg	125/78 mm Hg	Disappeared 70% Altered 30%	18 2

*Presented at The National Research Council Conference on the Physiology of Induced Hypothermia

TABLE XV*

Effect of Procaine Block of Atrial-Superior Vena Caval Area Upon Incidence of Ventricular Fibrillation in Hypothermic Dogs

Untreated Controls				Treated (Procaine Block)			
No of Dogs	Temp Range (° C)	Inflow Occlusion Time (min)	Per cent Fibrillation	No of Dogs	Temp Range (° C)	Inflow Occlusion Time (min)	Per cent Fibrillation
Stimulation Rough External Manipulation or Finger Massage of Ventricular Septum							
6	24.5 to 27	4.8	100	8	23.5 to 27.5	10.4	0
Stimulation Right Ventriculotomy, or Right Ventriculotomy and Placement of Sutures in Ventricular Septum							
6	27 to 28	4.2	100	11	24.6 to 28.3	10.4	0
16	19.5 to 22.5	8.2	56	16	19 to 22.5	10.3	6

*Presented at The National Research Council Conference on The Physiology of Induced Hypothermia

The duration of the P wave changes was approximately 10 minutes in the normothermic animals and approximately 20 minutes in the hypothermic dogs

Horvath What was the temperature of these dogs?

Shumacker These dogs had been cooled in cracked ice until the temperature reached approximately 31°C Then they were removed from the ice bath and the temperature continued to drift downward so that at the time of venous inflow occlusion, most of them had achieved a rectal temperature of approximately 26° or 27°C

Ferrer Dr Shumacker, am I correct that your technique involves the injection, not just at the junction of the superior vena cava and the appendage but throughout that area which was in dotted lines on your initial slide, an area which to my mind involves certainly a good upper third of the atrial wall on that side, is that correct?

Shumacker That is correct and, as I said a moment ago, we persisted with the injection until a slowing of the pulse rate and P wave changes were observed Some other workers have repeated our experiments and have not consistently obtained electrocardiographic changes

In Table XV are summarized briefly the results of some of our studies Let us consider first those animals in which moderate hypothermia was utilized and not those with more severe degrees of hypothermia In one group of experiments after the animals had been properly cooled and a thoracotomy performed the vena cavae were occluded, and the heart was manipulated very roughly either by squeezing it and striking it from the outside or by vigorous massage of the ventricular septum with a finger introduced through the right atrial appendage and through the tricuspid valve In these animals the rectal temperature at the time of such manipulation ranged from 23 5° to 27 5°C All of the control animals developed ventricular fibrillation after an average period of a little less than 5 minutes of venous inflow occlusion In contrast, those animals in which a procaine injection had been carried out withstood the cardiac trauma without fibrillation The average time of the venous inflow occlusion was approximately 10½ minutes

Experiments were then performed in a similar fashion except that the stimulus was either venous inflow occlusion and a simple right ventriculotomy, or venous inflow occlusion, right ventriculotomy and placement of sutures in the ventricular septum These animals were cooled to approximately the same degree, the tem-

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Effect of Procaine Block of Atrial-Superior Vena Caval Area Upon Incidence of Ventricular Fibrillation in Hypothermic Dogs

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Stimulation Right Ventriculotomy, or Right Ventriculotomy and Placement of Sutures in Ventricular Septum							
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16	19.5 to 22.5	8.2	56	16	19 to 22.5	10.3	6

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Experiments were then performed in a similar fashion except that the stimulus was either venous inflow occlusion and a simple right ventriculotomy or venous inflow occlusion right ventriculotomy, and placement of sutures in the ventricular septum These animals were cooled to approximately the same degree the tem

perature range being from 24 6° to 28 3°C Again, all of the untreated control animals developed ventricular fibrillation This occurred after an average inflow occlusion time of 4 2 minutes In contrast, none of the animals with procaine injection develo[ped] ventricular fibrillation The average inflow occlusion time in t[his] group was approximately 10½ minutes

The number of animals in this particular study is not very grea[t] We have carried out similar experiments in many more animal[s] but have not included them for statistical analysis because the differences were so clear cut in this initial study, the incidence of ventricular fibrillation being 100 per cent in the controls and zero in the treated animals Furthermore, by the time this study was completed, one of my assistants, Dr Radigan, had moved to the National Heart Institute in Bethesda and had begun to repeat the work He and his associates obtained essentially the same results approximately 100 per cent fibrillation in untreated controls and almost complete protection in the treated animals

We subsequently repeated the same experiments but carried the animals to lower body temperatures In these animals the rectal temperatures ranged between 19° and 22 5°C For some reason which is not clear to me, only 56 per cent of the control animals developed ventricular fibrillation during obstruction of the vena cava and right ventriculotomy Only one of 16 animals similarly treated but protected by procaine injection developed ventricular fibrillation

It seemed quite clear then that when one carried out an anesthetic blockade and obtained the characteristic slowing of pulse and alteration in P wave, a great deal of protection against ventricular fibrillation was afforded Under these conditions one could cool an animal obstruct venous inflow to the heart for approximately 10½ minutes, open the ventricle widely, place sutures in the septum or otherwise stimulate the heart, and prevent fibrillation in almost all animals

Lewis Did the controls have a saline injection?

Shumacker Yes, in a number of experiments the operator was given a syringe, the contents of which were unknown to him In some instances the syringe contained one per cent procaine, in others only normal saline solution The majority of those animals which had injection of normal saline developed ventricular fibrillation just as did the untreated controls A smaller percentage of them did not undergo ventricular fibrillation and we thought that

we might very well have achieved a block simply by mechanical distention of the tissues with saline

Sweet Was there any change in the P waves in those controls, then?

Shumacker Those animals injected with saline solution in which fibrillation did not occur had some alterations in their P waves

Lewis What about recovery of those that did not fibrillate? Did they all recover?

Shumacker They all did recover Dr Lewis, but we did not keep them for long periods of time Many were sacrificed within a few days I am sure you have reference to the fact that one can carry an animal through such a procedure as I have described and have him die later on Dr Radigan, Dr Lombardo, and Dr Morrow (11,12) recently presented some data on long term survival after similar experiments When ventricular fibrillation occurred, they restored a normal sinus rhythm by electric shock They reached the conclusion that the administration of a rapid acting digitalis preparation increased the long-term survival rate and concluded that late deaths in such experiments were probably the result of myocardial failure

By the time our studies had advanced to this stage they had been confirmed not only by Dr Radigan and his associates at Bethesda but also by Dr Hufnagel* in Washington The question arose whether the protection we had noted was a specific effect of sino-auricular node blockade or whether it was caused by anesthetization of the extrinsic nerve supply to the heart We therefore carried out additional experiments In one group a complete sympathetic denervation of the heart was achieved by surgical excision of the upper dorsal sympathetic chains and the stellate ganglia Table XVI When such animals were subjected to hypothermia of approximately 26° or 27°C, venous inflow occlusion for 10 minutes, right ventriculotomy, and placement of sutures in the ventricular septum, none of the animals developed ventricular fibrillation We then attempted to produce a sympathetic blockade by the intravenous or inter atrial administration of arfonad in doses sufficient to produce a significant drop in blood pressure Again remarkable protection was observed Only 13 per cent of 15 animals developed ventricular fibrillation

We also performed a bilateral vagotomy by sectioning the cervical vagosympathetic chain Almost all of these animals developed

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*Hufnagel C H Unpublished data

TABLE XVI*

Effect of Extrinsic Cardiac Innervation Upon Incidence of Ventricular Fibrillation in Dogs Cooled to Approximately 26° to 27°C and Subjected to Venous Inflow Occlusion for 10 minutes, Right Ventriculotomy, and Placement of Suture in Ventricular Septum

Type of Alteration of Nerve Supply	No of Dogs	Per Cent Developing Fibrillation
Bilateral upper dorsal sympathetic and stellate ganglionectomy	15	0
Injection of intra atrial or intravenous arfonad	15	13
Bilateral section of cervical vago sympathetic trunks	15	80
Stimulation of the right vagus	15	33 (entire group) 17 (excluding three in which vagal escape occurred)
Bilateral division of vagi distal to caudate ganglia	15	20
Bilateral upper dorsal sympathetic and stellate ganglionectomy and bilateral division of cervical vagosympathetic trunks	15	40

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*Also presented at The National Research Council Conference on The Physiology of Induced Hypothermia

ventricular fibrillation under the circumstances of the experiment Dr Swan s group (13) had previously published a report in which they found that stimulation of the right vagus nerve seemed to confer some protection against ventricular fibrillation We re peated these experiments and got essentially the same results There were 15 animals in this group One third of them did de velop ventricular fibrillation However if we exclude three animals in which vagal escape obviously occurred the rate of ventricular fibrillation was only 17 per cent

Sympathetic blockade either by sympathetic denervation or the administration of arfonad and vagal stimulation therefore seem to offer a great deal of protection against ventricular fibrillation

When an upper dorsal sympathectomy and stellate ganglionec tomy were performed and in addition the vagosympathetic trunks in the neck were divided we found the rate of fibrillation to be approximately 40 per cent In these animals both the vagal and sympathetic nerve supply to the heart had been severed The only experiments which are shown in Figure 125 which are not under standable to us are those which relate to bilateral division of the vagi distal to the caudate ganglia Here we found a fibrillation rate of only 20 per cent When the vagi are sectioned distal to the caudate ganglia the cardiac depressor nerves are left intact We wondered whether section of the vagus nerves in this location might bring about an axonal reflex but we obtained no evidence that this was the case since there was no slowing of the heart rate or other evidences of vagal stimulation

Sweet May I ask where the caudate ganglion is? I am afraid I do not know the anatomy of your animal

Shumacker The dog has a very peculiar vagosympathetic path way It is a common one in the neck As the vagosympathetic trunks begin to separate into purely sympathetic and vagal fibers there is seen on the one hand the large stellate ganglion which continues down the anterolateral aspect of the vertebral bodies as the upper dorsal sympathetic chain Near the stellate ganglion and attached to the vagosympathetic trunk above and the vagal nerves below is another ganglion which is called the caudate ganglion

One other problem that concerned us was that of coronary air embolism (Table XVII) This is a serious matter even in normo thermic animals It is a much more difficult problem in the hypo thermic state I may summarize our experiences by saying that certain measures permit the achievement of a satisfactory conver

TABLE XVII*

Experiences With Treatment of Coronary Air Embolism and Ventricular Fibrillation in the Hypothermic Dog by Cardiac Massage, Intracardiac Epinephrine, and Electric Shock

No of Dogs	Temp of Dogs (°C)	Average Volume Air Injected (ml)	Average Interval Between Injection of Air and Onset of Fibrillation in Minutes	Average Duration of Fibrillation in Minutes before Institution of Massage	Average Period of Massage in Minutes Necessary for Clearing Coronaries of Air	Average Duration of Fibrillation in Minutes	Remarks
Sino auricular Node Injection Prior to Expected Onset of Fibrillation							
4	26 to 26 5	4 9	4 8	2 5	2 1	9	One did not fibrillate others resuscitated
Sino-auricular Node Injection After Onset of Fibrillation							
6	26 to 26 5	3 9	2	3 3	5 3	9 8	Fibrillation in all all resuscitated
No Sino-auricular Node Injection†							
10	25 to 26 5	4 2	0 8	4 75	2 3	13	Fibrillation in all one had fibrillation twice two 4 times all resuscitated

† One had injection of the sino auricular node after fibrillation recurred 4 times

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sion to a sinus rhythm when ventricular fibrillation is induced in the hypothermic animal by the injection of air into the coronary arteries It is necessary to remove all of the air from the coronary arteries Sometimes this can be done simply by vigorous cardiac massage If small amounts of air remain in certain coronary arteries it is possible to cut across the terminal twigs of these coronary branches and milk the air out of them At the completion of the experiment the divided terminal arterial twigs are ligated with fine silk transfixing ligatures It is necessary to obtain a very vigorous ventricular fibrillation before utilizing electric shock If the fibrillation remains weak in spite of adequate cardiac massage and the removal of air from the coronary arteries it can be made quite strong by administering a small amount of very dilute epinephrine solution into the heart This is a maneuver which Dr Lewis has employed with success

While doing these experiments we obtained some suggestive evidence that anesthetic blockade of the superior vena caval atrial junction may be of some benefit in this particular problem For example we found that the introduction of air into the coronary arteries in the unprotected hypothermic dog invariably brought about ventricular fibrillation In four animals the superior vena caval atrial junction was infiltrated with procaine solution before the expected onset of fibrillation One of these animals did not develop ventricular fibrillation In six animals the procaine injection was carried out after the onset of fibrillation All were successfully resuscitated and fibrillation did not recur Of ten animals in which no procaine injection was carried out either before or after the onset of fibrillation recurrence of fibrillation was noted after conversion in three animals In one fibrillation occurred twice in two four times All of them were ultimately resuscitated

As shown in Table XVIII animals can be resuscitated even when coronary air embolism is induced in the hypothermic animal and a right ventriculotomy and placement of sutures in the ventricular septum are carried out When procaine injection was accomplished in four animals after the onset of ventricular fibrillation no recurrence of fibrillation was noted after conversion Recurrence of fibrillation was noted in two of four animals in which no injection was made Fibrillation recurred three times in one of them and ten times in another In the last animal mentioned the final successful defibrillation occurred only after procaine injection was carried out

TABLE VIII*

Experience with Treatment of Coronary Air Embolism and Ventricular Fibrillation in Hypothermic Dogs Subjected to Right Ventriculotomy and Placement of Sutures in Ventricular Septum by Cardiac Massage, Intracardiac Epinephrine, and Electric Shock

No of Dogs	Temp of Dogs (°C)	Average Volume Air Injected (ml)	Average Interval Between Injection of Air and Onset of Fibrillation in Minutes	Average Duration of Fibrillation in Minutes before Institution of Massage	Average Period of Massage in Minutes Necessary for Clearing Coronaries of Air	Average Duration of Fibrillation in Minutes	Remarks
Sinoauricular Node Injection After Onset of Fibrillation							
4	26 to 27	4 1	2 2	5 6	2 2	7 5	Fibrillation in all, no recurrence of fibrillation All resuscitated
No Sinoauricular Node Injection							
4	25 5 to 27	4 4	1 1	5 2	2	27	Fibrillation in all, fibrillation recurred 3 times in one, 10 times in another† all resuscitated

† Before the last successful defibrillation sinoauricular node was injected

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Utilizing the information which we had obtained from all of these experiences, we were able to perform a right ventriculotomy in hypothermic animals, make a ventricular septal defect, and close it by suture without any mortality

The combined experience of my own group, that of Radigan and his associates, and that of Hufnagel is now large and offers convincing evidence that the injection of an anesthetic agent about the superior vena caval atrial junction offers real protection against ventricular fibrillation These studies also indicate that sympathetic blockade by operative denervation or the administration of arfonad and right vagal stimulation also offer real protection

I would like now to say a few words about another problem which is related to the use of acutely induced hypothermia as an aid for intracardiac surgery One of its disadvantages for certain types of intracardiac procedures was the brevity of reasonably safe venous inflow occlusion Most individuals feel that this safe period is somewhere around 10 12, or perhaps 15 minutes and few have dared to maintain venous inflow occlusion in patients for more than 6 or 8 minutes This is time enough, as Dr Lewis and others (14) have demonstrated amply in patients, to permit closure of an atrial septal defect, or to do an open pulmonary valvulotomy It may not be a sufficiently long period for the careful closure of a ventricular septal defect or the combination of this procedure with the correction of an infundibular stenosis

In some experiments which are not yet published, my associates and I have found that the safe period of inflow occlusion can be increased greatly by combining hypothermia and blockade of the superior vena caval atrial junction with the perfusion of oxygenated blood into the coronary arteries alone, or, better still into the coronary and carotid arteries In these experiments the blood to be used had been fully oxygenated by bubbling oxygen through it It was perfused by gravity, ordinarily at a rate of about 25 or 30 drops per minute When only the coronary arteries were perfused, a small catheter was introduced into the ascending aorta and the aorta was clamped distally so that the catheter communicated with none of the branches of the arch of the aorta but only with the proximal portion of the aorta and the coronary arteries In experiments in which the coronaries and the carotids were both perfused, a plastic tube was introduced into the aorta through the left subclavian artery The right subclavian artery was temporarily occluded, as was the aorta distal to the origin of the left subclavian artery When both the brain and the coronary arteries were perfused, the

animals maintained a nice pink heart during long periods of venous inflow occlusion Up to the present the longest period of vena caval obstruction is 39 minutes, and the shortest, I believe, about 25 minutes A few of those animals in which heparinized oxygenated blood was used died postoperatively from hemorrhage Most of the animals recovered and they had no visible evidence of any neurological sequelae A few animals which were examined postoperatively by electroencephalographic study had normal electroencephalograms These animals have been kept for long periods of time and the group is rather sizable

There was only one exceptional animal in which there was evidence of brain damage In this animal a slower perfusion rate was used than in the others and venous inflow occlusion time was approximately 38 minutes

Lewis At what temperature?

Shumacker The temperature in these experiments was about the same as that used in the majority of the other experiments described around 26° or 27°C

One of the most interesting aspects of this study is the fact that when we perfused the coronary arteries alone, we were able to carry out venous inflow occlusion for periods of from 25 to 30 minutes, with ultimate survival of almost all of them and with apparently complete recovery from any transient neurological signs which might have been present soon after the operation In the first group of twelve dogs all survived except one which died postoperatively of hemorrhage In contrast, however, to those treated by both coronary and carotid perfusion approximately half of these animals did show immediately after operation some evidence of neurologic damage, either hindleg weakness or stupor These signs were present for from 1 to 3 days after which behavior and function appeared normal in all

Since the ultimate good results were similar in the two groups this study would suggest that the survival of these animals without neurologic sequelae following long periods of venous inflow occlusion was to a significant degree dependent upon maintenance of the heart in good condition during the vena caval obstruction rather than upon brain perfusion alone The fact that those animals with both coronary and carotid artery perfusion with oxygenated blood did even better demonstrates, however, that brain perfusion itself also is protective

Finally I should like to say a word about the use of citrated blood In a considerable number of experiments in which the

oxygenated blood was heparinized we experienced great difficulty in securing hemostasis in spite of the use of protamine at the conclusion of the perfusion For this reason, we used citrated oxygenated blood in a number of animals This worked very well, in spite of the fact that a number of other workers have felt that perfusion of the coronary arteries with citrated blood was incompatible with survival When one uses citrated blood, the heart rate is noted to slow rapidly once the perfusion is begun and soon a complete cardiac arrest takes place The heart remains very pink during the entire period of perfusion When the venous inflow occlusion is terminated, very often a sinus rhythm returns with simple cardiac massage If it does not a small amount of calcium is injected into the ventricle and massage is continued Then a sinus rhythm is restored

When the coronaries are perfused with heparinized blood the dog's heart continues to beat during the entire period of venous inflow occlusion and coronary perfusion By the end of the perfusion period the heart is not quite as pink as is the arrested heart in the animal being perfused with citrated blood

It is impossible to say at the present time just how useful the information derived from all of these experiments will prove in patients From our small experience and the somewhat larger experience of Dr Morrow and his associates, and of Dr Hufnagel, it would seem fair to conclude that anesthetic blockade of the right atrial-superior vena caval junction affords the patient protection against ventricular fibrillation in the hypothermic state just as it does in the case of the dog As Dr Hufnagel has emphasized, it is better to use a longer lasting anesthetic than procaine, xylocaine for example

I believe there is good reason also to believe that coronary and carotid artery perfusion with oxygenated blood will prove useful in patients and will permit a longer safe period of venous occlusion with recovery At the present time I do not know of any clinical experiences to report I have used the method in only one patient, and this patient's anatomical situation was such a complicated one that the fatal outcome seems better related to this matter than to the hypothermia and perfusion technique itself

Montgomery Did you mean the heart when it became somewhat discolored, was a little bit cyanotic?

Shumacker When one perfuses the coronaries with oxygenated heparinized blood and cardiac arrest does not occur, one notices

as the experiment goes on for 20, 30, or 40 minutes, that the cardiac contractions get progressively weaker and the heart muscle becomes faintly cyanotic in appearance

Montgomery If the cyanosis is identifiable, this seems a rather good opportunity to learn whether the perfusion of cooled blood probably equilibrated against oxygen will correct the cyanosis

Shumacker The blood is fully oxygenated

Montgomery That is, it is all oxygenated, none is air-equilibrated?

Shumacker The blood is completely oxygenated In contrast to the faint cyanosis that ultimately appears in the dog's heart which is working, though at a markedly reduced rate, during the per fusion with heparinized blood, the heart which is being perfused with citrated blood and which is at complete rest remains bright pink throughout the entire period of perfusion and vena caval occlusion I must say that I do not know whether it will prove to be as safe to use citrated blood for this purpose in humans as it has proved in dogs

Crisman Is it stopped in systole?

Shumacker I am sorry but I cannot answer that question

Lewis In our experience with citrated blood, we obtained ven tricular fibrillation uniformly, and I think Cookson (15) had the same experience, too It was a rather surprising difference, other wise, I think our coronary infusion experiments have been much like yours At 25°C, coronary perfusion would provide 20 minutes of cardiac inflow interruption with a ventriculotomy, regularly, but when we tried to increase the circulatory interruption time to 30 minutes at 25°C, we started getting hindlimb paralysis in some of the dogs

One other observation we made was that we could use hepa rinized unoxygenated blood The arteriovenous oxygen difference between the coronary sinus and the perfused blood was still sig nificant, and we concluded that the cold heart could still extract a fair amount of oxygen

Shumacker I am glad that you brought this matter up In some of our experiments we also used blood that was not fully oxygenated with good results We had some ventricular fibrillation both in the group of animals perfused with fully oxygenated blood and that perfused with incompletely oxygenated blood In both we found that we could bring about successful conversion

Lewis This did not get rid of fibrillation in our experience, either We still had it in the perfused animals undergoing ventricu lotomy

As far as your very interesting work on the use of sinoauricular node block to prevent fibrillation is concerned, I think your evidence is very impressive. We have not used this technique and hence have not confirmed your results, but in our own laboratory, the use of a ventriculotomy as a test operation for ventricular fibrillation has been rather a complex procedure. One of the variables that is hard to eliminate is that of skill in the man who does the ventriculotomy. Some of the residents who worked with me have been able to do ventriculotomies with a very low incidence of fibrillation while others, learning the operation, get fibrillation almost every time until they learn how to do a ventriculotomy. We have tried to do the ventriculotomy carefully without getting fibrillation. You, on the other hand, tried to produce fibrillation. At any rate, in our total experience with right ventriculotomy, not as a test operation but for intracardiac procedures like ventricular septal defects, we have never had a 100 per cent incidence of fibrillation. It was about 45 per cent in 80 or 100 dogs.

Because we are so impressed with the matter of skill, we are trying to set up these experiments so that the surgeon doing the ventriculotomy does not know what factors, such as the mixture of respiratory gases, have been altered in the experiment. We hope that this will provide a valid control. Actually, I think it is almost as difficult to get an adequate control in some of these experimental operations as it is in clinical experiments.

Montgomery: What do you feel is the optimum gas mixture for use in surgery in the dog or in man in hypothermia now? Is it oxygen with 5 per cent CO_2?

Lewis: We use 5 per cent CO_2 in oxygen.

Shumacker: This is a most important problem and my group has not made any effort to determine what gaseous mixture is ideal. In all our experiments we used 100 per cent oxygen. I am sorry that in order to present the material as briefly as possible I did not mention the fact that Dr. Lewis and others have also been working with coronary and brain perfusion. Gertner and his colleagues (16) from Baltimore recently reported some experiences at the meeting of the Surgical Forum of the American College of Surgeons. They used a mechanical pump instead of gravity flow. The results were rather comparable.

Montgomery: The perfused blood to the coronary and brain was at room temperature?

Shumacker: We just took them out of the refrigerator.

Montgomery They were way down, then?

Shumacker I don't know We did not make careful temperature measurements of blood being perfused I am sure the temperature in each bottle varied considerably during the course of the perfusion Our room temperature was about 22°C

Simeone What was your anesthesia?

Shumacker All of the animals were anesthetized with thiopental sodium, intubated, and were carried on 100 per cent oxygen delivered by a mechanical insufflator During the vena caval occlusion the respirations were stopped

Dr Stone and his associates (17) from the University of Pennsylvania reported some very interesting experiments at the last meeting of the American College of Surgeons Cerebral blood flow and cerebral metabolic activity were measured in patients under hypothermia They observed with hypothermia a drop both in cerebral blood flow and in cerebral metabolism The metabolic activity of the brain did not decrease quite as much as did the cerebral blood flow One thing which seemed significant was the observation that during hypothermia cerebral metabolism increased very markedly whenever shivering took place in these hypothermic patients I note that the average cerebral blood flow decreased from 41 ml per 100 grams per min to 12 ml The average cerebral vascular resistance rose from a control of 1 9 to 7 4 resistance units The cerebral metabolism decreased from 2 8 ml of oxygen per 100 grams per min to 0 93 ml When shivering occurred, even at 80°F, the cerebral metabolism increased over the resting control level

Horvath Everything else increases so it is hardly surprising

Shumacker No but it does demonstrate that just because the animal or patient is cooled, one cannot assume that the metabolic activity will remain at a level low enough to be compatible with a substantial reduction in blood flow

Horvath What is that again?

Shumacker In these patients, you understand, the cerebral blood flow was markedly decreased and so was the metabolic rate

Horvath During shivering also?

Shumacker They pointed out, as I recall it, that the cerebral metabolic activity increased with shivering, but I do not recall any comment about what happened to cerebral blood flow under such circumstances

Horvath The hepatic blood flow goes up if the animal is shivering If it is not shivering it goes down Cerebral blood flow has also gone down when they were not shivering so this increased oxygenation I am sure must be correlated to some extent with an increase in flow Whether it goes back to normal or not or to above normal I do not know but it certainly is related to it

Burton With regard to your protection from fibrillation by sympathectomy it is interesting that some work by McEachern Hall and Manning (18 19) on experimental coronary occlusion in dogs showed a very marked protective effect of sympathectomy in preventing fibrillation which was the event that led to the "early death of these animals

Shumacker We have been doing some similar studies We have not as yet analyzed the results of these experiments but I believe that they are going to show that sympathetic denervation does decrease the incidence of ventricular fibrillation when the left anterior descending branch of the coronary artery is divided between ligatures at the point of its origin

Burton As I remember it they did get an effect of a blocking agent but not as good as they hoped for This would agree with your experience wouldn t it?

Shumacker Yes The principal disadvantage of the anesthetic blockade of the right atrial superior vena caval junction is that sometimes one utilizes hypothermia for conditions which do not permit one to carry out this injection As examples I might cite a very ill patient with tetralogy of Fallot who it is thought will withstand a pulmonary systemic shunt operation better under hypothermia than under normothermic conditions or the patient who is being operated upon for some cerebral difficulty under hypothermia We have used the intravenous administration of arfonad in a few patients operated upon under hypothermia for resection of a thoracic aortic aneurysm Ventricular fibrillation did not occur in this small experience

Horvath Cookson about 4 years ago reported autonomic blocking agents are effective in preventing fibrillation (20)

Sweet I wanted to ask you a little about the autonomic blocking because Botterell and associates (21) have made this observation Of the patients on whom they were operating for an intracranial aneurysm in the hypothermic state the only two who went into ventricular fibrillation had just had a rather marked fall in blood pressure produced by arfonad I see that when you gave

this drug you produced rather substantial falls to an average systolic level of around 60 mm Hg Did you give the agent so as to bring about the drop fairly gradually and then maintain it at that level? Do you recall offhand your exact tactic in provoking the drop in blood pressure? Perhaps it was not standardized

Shumacker In the animal experiments we used arfonad in sufficient dosage to bring about a substantial drop in blood pressure This was administered just before vena caval occlusion and of course during vena caval occlusion arterial blood pressure was not maintained

In the few human patients with thoracic aneurysms in which I have used arfonad a very marked drop in blood pressure was deliberately achieved I feel confident that none of the methods I have mentioned provides absolute protection and I am not surprised that Dr Sweet knows of two clinical cases in which fibrillation did occur during the administration of arfonad

Simeone In your animals Dr Shumacker I gather you did not use so much arfonad that you got a very sizable drop in blood pressure is that right?

Shumacker It was a rather sizable drop On the average the blood pressure was reduced from a systolic pressure of 153 to 60 mm Hg

Sweet I might make one more comment I am sure you are aware of this but with regard to perfusing the brain in man it does not of course suffice to put the blood into one carotid One would have to take the trouble in man to put it in the ascending arch of the aorta

Shumacker That is essentially what we did We placed the plastic tube into the arch of the aorta through the left subclavian and we occluded the other subclavian at the point of its origin and the thoracic aorta just distal to the point where it gives off the left subclavian This is not difficult to carry out in a patient It takes only a short while to isolate both subclavian arteries and the aorta if one has a bilateral thoracotomy with transection of the sternum

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CLINICAL APPLICATION OF HYPOTHERMIA DURING OPEN HEART SURGERY

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Hypothermia for clinical use has undergone periods of popularity in the past and then faded out, but perhaps the present enthusiasm for its use will be more lasting It will take some time to tell, of course Our main interest in the use of hypothermia has been as an aid for doing open intracardiac surgery Following the work of Bigelow (1) and Boerema (2), we began to study the use of moderate degrees of hypothermia (about 26°C) in order to do open heart operations in dogs

With hypothermia we learned to operate successfully on both the atrial and the ventricular septum, within all four chambers of the heart, and on all of the valves of the heart After we had developed a successful technique for operations on the atrial septum in dogs, we started using that method to repair atrial septal defects under direct vision on man a little over 3 years ago

Since then, we have used the method to do open intracardiac operations on 49 patients In addition, we have used it on three patients with extracardiac operations We have also used hypothermia to do a few cancer operations including four total right hepatectomies and one pelvic evisceration done while the aorta was occluded to provide hemostasis In addition we have used surface cooling to treat 25 desperately ill patients with high fevers, something in the manner of the technique used by Laborit (3) and known as 'Artificial Hibernation" in France

Since there has been considerable interest in the presentations of Dr Smith and Dr Andjus I thought I might go into more detail concerning our somewhat similar work in deep hypothermia and merely describe the clinical work rather briefly to begin with If there is any interest in particular aspects of this clinical work, I will, of course, be glad to enlarge upon it



FIGURE 126. An anesthetized patient is shown wrapped in the cooling blankets. The machine which cools the antifreeze solution and pumps it through the blanket is out of the picture. Reprinted by permission from Lewis, F. J., Varco, R. L., and Taufic, M.: Repair of atrial septal defects in man under direct vision with the aid of hypothermia. *Surgery 36*: 538 (1954).

Our biggest experience has been in repairing interatrial septal defects and so I will describe the method we have used for that operation We anesthetize the patients with pentothal and flaxedil (a type of curare preparation) and then after attaching electro cardiograph leads and thermometers we cool the patients with surface cooling as shown in Figure 126 Though we have used both arteriovenous shunt cooling and surface cooling in animals we have used only surface cooling in man and we usually cool the patient by applying special blankets at a temperature of −4°C This is a relatively slow type of cooling in comparison with that used by some other clinicians and it may take as long as 3½ hours to reduce the body temperature to 30 C the level at which cooling is discontinued and operation started During the operation the temperature drifts down to a level between 24 5 and 29 5°C

The patient s chest is opened through a bilateral transverse incision with division of the sternum and entry into both pleural cavities This provides an excellent exposure of the entire heart Then preparations are made for the cardiotomy Perhaps the most important step in these preparations is the digital exploration of the interior of the heart which is done by inserting a finger into the right atrium or in some more complicated cases into both the right and the left atria In this way we can get a fairly good understanding of the surgical anatomy of the defect ahead of time and thus plan the repair to be done during the open cardiotomy quite precisely

Following the exploration we set up our instruments and rehearse the team Each stitch that is to be used and each step of the operation is discussed Finally the circulation is interrupted by occluding the superior and inferior vena cavae Following this both pulmonary roots are occluded with a tourniquet in order to stop any drift of blood into the atria during the cardiotomy which might otherwise partially obscure the field

The repair is then completed and as the last stitch is placed the left side of the heart is filled with saline injected through a small plastic tube which is inserted into the left atrium through the repair This is to prevent air embolism

I should mention that we also employ another precaution to avoid air embolism The outflow of the heart as well as the inflow is interrupted during the cardiotomy and this is done with a clamp one arm of which is placed through the transverse sinus of the heart When this clamp is closed both the aorta and pulmonary

artery are occluded After the left side of the heart is filled with saline the right side is filled by releasing one of the cavae and the atrial wound is then closed with a clamp After this the circulation is restarted by simply releasing the various clamps and ligatures

The length of circulatory interruption has ranged from 3 to 7½ minutes The median time of circulatory interruption was 4.5 minutes After the chest is closed the patient is rewarmed in a bath of water at 45°C Rewarming in the bath has taken from 15 minutes up to an hour and a half

The atrial septal defects we have closed are listed in Table XIX according to anatomical type For the surgeon who is going to do this type of surgery the special pathologic aspects are of great importance The anatomic characteristics of these various types are distinct and the techniques of closure needed vary considerably Some of the defects are complex whereas others are simple openings which can be closed easily with a continuous stitch

To us probably the most interesting defect has been the high defect listed in Table XIX These high defects are completely separate from the foramen ovale and they lie just beneath the superior vena cava They are invariably associated with partial anomalous pulmonary venous drainage thus making the repair difficult The pulmonary blood must be accurately diverted into the left atrium

From another point of view the low or ostium primum defects are difficult too for in repairing them it is quite easy to injure the conduction system All three patients with this defect have had complete heart block at one time or another after the repair In general however the results of operating on atrial septal defects have been good and the defects are apparently completely closed at least in most of the cases We have done postoperative cardiac catheterization studies on 22 of the patients and with the exception of one case none of them has shunts remaining This exception was the first high defect we encountered and it is now apparent that we missed a high anomalous pulmonary vein which entered the superior vena cava

There were five deaths Two deaths are largely attributable to the cold for the patients died primarily of ventricular fibrillation One death was caused by heart block one to postoperative hemorrhage and one to a technical error Three of the deaths were in adults but most of the patients have been adults

TABLE XIX
Surgery for Atrial Septal Defects

	No of Patients
Foramen ovale defects	27
High defects	9
Continuous defect	1
Persistent ostium primum	3
Unknown (heart not opened)	1
Total	41
	(5 deaths)

The median age is 23 and twelve of the patients were over 30 The oldest patient, aged 61, was a successful case Hypothermia is quite safe for adults, though it is probably safer for infants and children

This method of doing open intracardiac surgery is mechanically simpler than the other methods and a mechanical breakdown is never catastrophic Then, as another advantage, it requires a relatively small surgical team, so the responsibility of being in a position where a fatal human error can be made falls to only a few people Furthermore, complexities of shunting the blood outside of the body are avoided, and finally this method provides a drier operating field than other methods for operating inside the heart

The method has two principal disadvantages One is the limited time allowed for an intracardiac operation This handicap can be overcome, at least partially, by exploring the heart as I described and by planning the intracardiac repair carefully beforehand Even fairly complex defects can be repaired in a few minutes We have recently successfully repaired a triatrial heart, a very unusual defect, and we have also repaired successfully a heart with total anomalous pulmonary venous drainage in which all of the veins entered the right atrium This latter repair required first the construction of an atrial septal defect, and then the reconstruction of the right atrium to divert the four pulmonary veins through the newly created atrial septal defect into the left atrium without obstructing the cavae The child who was formerly cyanotic, now

appears to be normal, he has a much smaller heart and is no longer cyanotic

Fairly complex operations can be done within the time limits of moderate degrees of hypothermia but there are methods of extending the time limitation if more time is required One method is by adding coronary perfusion Dr Shumacker has mentioned this We have studied this technique experimentally and used it for two atrial septal defect repairs but it may be unnecessarily complex at least for this particular type of heart operation

The time period allowed for total inflow occlusion can also be extended by using deeper levels of hypothermia but when deeper levels of hypothermia are used the incidence of ventricular fibrillation tends to increase This brings us to the second main disadvantage of hypothermia for open cardiac surgery the tendency of the heart to develop ventricular fibrillation

Among the first thirty two patients upon whom we did open heart operations there were eleven cases of ventricular fibrillation a high incidence All except one of these hearts was successfully defibrillated but nonetheless it is a complication we would like to avoid

In order to investigate this complication experimentally we tried to devise a modification of Wiggers's (4) experiments in which a measured electrical shock coming in late systole was used to produce ventricular fibrillation This we did by taking the pulse from an electrocardiograph machine through an electronic device to trigger a Grass stimulator A delay in the Grass stimulator allows one to place the shock at a precise time during the cardiac cycle The height of the QRS complex is used to trigger the Grass stimulator and with a delay of about 150 msec it depends on the heart rate of course as the ventricles can be shocked during the period of late systole when the heart is particularly sensitive

These are rather complex experiments and we gave them up when we started getting a paradoxical result We found that it was harder to produce fibrillation in the cold heart than it was in the warm heart It seemed apparent then that this was not the type of fibrillatory stimulus we had to worry about when operating on the cold heart

For the next experiment we used rats because a large number of animals might be needed The rats were to be cooled until they fibrillated Then we could try various methods to reduce the incidence of fibrillation When we started working on these animals

we found to our dismay that they did not fibrillate easily Dr Suad Niazi, who did this work, found that they went into cardiac standstill but since they were rather expensive he did not want to discard them, so he tried to rewarm these cold, apparently dead rats, *and found, surprisingly enough that they could be revived* This work was done independently of the work that Dr Andjus described, but, as you will presently see, it has been quite similar in many respects We started these studies in 1953 (5), but, as you know, Dr Andjus's work (6) was started earlier Figure 127 shows the setup Dr Niazi devised for cooling rats to low body temperatures We have always used artificial respiration throughout the experiment The first respirator employed a small electric sewing machine motor The animal was cooled with blankets which can be lowered to temperatures below freezing difficulty

Table XX gives the results of Niazi's first experiments The rats were respired with compressed air, cooled until the heart stopped, and then rewarmed with hot water

The maximum time that the heart could be stopped with survival was about 3 hours Animals kept at temperatures below 10°C for 15 hours would occasionally have a resumption of heart beat but the animals never survived

Andjus What was the temperature range in which these animals were maintained?

Lewis All below 10°C

Andjus What do you mean by that?

Lewis The lowest was –3°C and the warmest was about 10°C The average was 5 3°C

This was quite a striking result, especially since we had not yet heard of Dr Andjus's accomplishments Our respirator had an inefficient cycle in which neither inspiration nor respiration took place using 1/3 of the cycle so we bought an electronically controlled respirator that is very efficient the length of expiration and inspiration can be controlled separately and there is no pause between inspiration and expiration

Smith What is the point of giving artificial respiration if you have stopped the heart?

Lewis After the heart has stopped beating for 5 minutes we discontinue the respiration It may be dangerous to continue it Some recent work of J H Gibbon's* with the heart lung machine

*Unpublished data given in a speech at Postgraduate Course on Cardiovascular Disease Clinical Congress American College of Surgeons Nov 2 1955

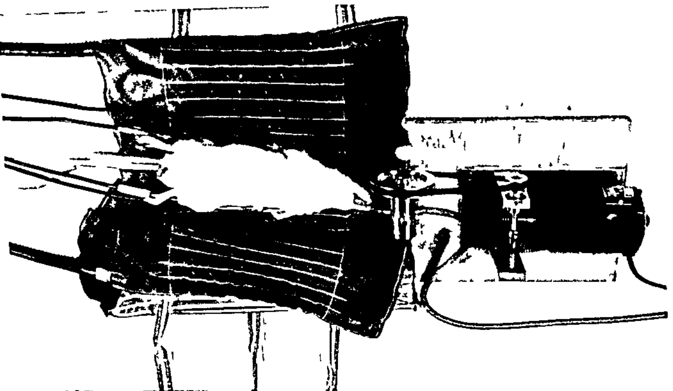


FIGURE 127 An anesthetized rat about to be wrapped in refrigerating blankets The respirator is attached to the intratracheal tube the thermometer is inserted, and electrocardiograph leads are in position Reprinted by permission from Niazi S A, and Lewis, F J Tolerance of adult rats to profound hypothermia and simultaneous cardiac standstill *Surgery* 36, 25 (1954)

TABLE XX
Survival of Rats After Cardiac Standstill at Low Body Temperatures

	Duration of Standstill	No of Animals	Deaths During Rewarming	Short Survival 1 to 24 hr	Short Survival 1 to 8 days	Long* Survival
I	35 to 44 min	12	0	0	7	5
II	1 to 3 hr	21	8	8	4	1
III	3 to 16 hr	14	10	4	0	0

*Kept for at least 2 months after cooling

Reprinted by permission from Niazi S A and Lewis F J Tolerance of adult rats to profound hypothermia and simultaneous cardiac standstill *Surgery 36* 25 (1954)

suggests that continuation of respiration while circulation through the lungs is stopped may produce an alkalosis in the respiratory membranes which causes a diminished gaseous exchange in the recovery period

With this new respirator and using oxygen Dr Niazi was not able to resuscitate animals cooled to cardiac standstill at these low temperature levels This was a perplexing finding but remembering the deficiencies of the first respirator he added carbon dioxide to the respiratory mixture and was again able to achieve approximately the same results as he had earlier

At the present time the technique is to anesthetize the rats with approximately 40 mg of pentobarbitol sodium per kilogram of weight and then cool them A transoral intratracheal tube is attached to the respirator and the animal is given 5 per cent carbon dioxide in oxygen at a respiratory rate of 30 per minute When the heart stops between 3° and 6 C the respiration is stopped as well

The animal is left in a state of cardiac and respiratory standstill for 2½ hours and then rewarmed by applying hot water to the chest until the heart starts beating The respirator is then started and hot water is applied to the entire body With this technique twenty of the last twenty four rats survived for at least 24 hours and sixteen have been long term survivors All of these last twenty four rats had transplanted cancers because we wanted to see if the deep cooling might kill the cancers To our surprise in twelve of

THE EFFECT OF CO_2 ON THE PREVENTION AND TREATMENT OF HEART BLOCK IN HYPOTHERMIC RAT

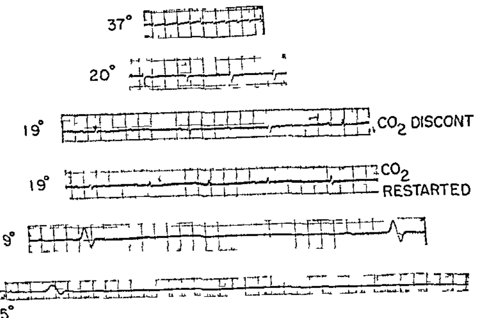


FIGURE 108 The effect of carbon dioxide on the prevention and treatment of heart block in the hypothermic rat. Body temperatures of the rat are shown at the left. Carbon dioxide was discontinued just before the temperature reached 19°C and complete heart is seen in the first tracing at 19°C. The second tracing at 19°C was made a few minutes after carbon dioxide had been restarted and it shows that a *sinus rhythm has returned*

the sixteen which survived cooling, the cancer regressed completely Among the twenty four controls the cancer regressed completely in only four Experiments of this type will have to be pursued further, but they illustrate a search of a possible practical use of the method

Montgomery Backing up Dr Temple Fay's work

Lewis This is a follow-up of Temple Fay's work (7) However, he was never able to cool his patients much below 26°C He used local cooling of a more intense degree and some tumors really regressed even though none of them was cured

Horvath Might I correct that statement a little bit? I think it was quite possible for Dr Fay to lower the temperature much below the 78°F he did but at that time it was not considered feasible from the standpoint of effect of low temperatures

Lewis This may be true, yes On reviewing Dr Fay's publications I have concluded that he probably would have reduced the temperature considerably below 78°F if he had been able to do this It is clear that he felt that temperatures of 40° to 50°F were more effective against malignant growths than higher temperatures For example, this is a quotation from a 1940 article (7) "With the continued biopsy evidence that degenerative changes could be produced to a marked degree by *local* refrigeration at temperatures between 40° and 50°F as reported by Smith and myself it was natural that attempt should be made to reach the deep structures which, of course were not influenced by local application of cold"

The electrocardiograph tracings in Figure 128 illustrate the effect of giving carbon dioxide to the rats Without carbon dioxide there is a high incidence of heart block and when the heart finally stops beating it stops at higher temperatures usually around 15°C With carbon dioxide there is less heart block and the heartbeat continues to lower temperatures before it finally stops This of course is an advantage

At 19°C in Figure 128 the carbon dioxide had been discontinued for a few minutes and a complete heart block resulted With carbon dioxide again a regular sinus rhythm was restored It continued even down to 5°C in this case

Horvath Do you think that is caused by the carbon dioxide or by artificial respiration?

Lewis Artificial respiration is at the same rate throughout

Burton But this is a tremendous overventilation which would lower the carbon dioxide enormously Perhaps you are just restoring the normal pH

Lewis I think that is true but we do not have pH determinations in these animals however we do have some in dogs which I will show you later

Another way of controlling the pH if that is the main mechanism as it probably is would be to change the respiratory rate appropriately It can be done of course by gradually slowing the respiratory rate but there are some practical disadvantages In human subjects for example if the alveolar carbon dioxide is followed with a mass spectrometer which is a fairly complicated technique and the respiratory rate and volume adjusted in order to keep the alveolar carbon dioxide at the level considered desirable the pH can be kept constant But then when the chest is opened the lungs collapse at that very slow respiratory rate Collapsed segments of the lung will shunt blood without allowing it to come in contact with alveolar air So it seemed more desirable to us to keep the lungs inflated with the chest open In order to do that the minute respiratory volume must be sped up

Horvath Were these animals chests open?

Lewis No

Horvath Then there is no comparison between the two groups of experiments I think one of the big problems with most of the hypothermia work is that what happens in open chest animals is compared with what happens in closed chests What happens in the open chest is described and then it is said that that is what should happen in the closed chest but those things are not at all comparable

Lewis No they are much different I agree

Horvath So the interpretation of the techniques used with open chest against closed chest will just give results that complicate the picture and just confuse the issue Certainly it has been true that people have been able to lower the temperature of animals just on air without any additional carbon dioxide

Lewis Not to these levels

Horvath Without hyperventilation Yes down to these levels

Lewis I know of no one who has lowered the temperature of animals to below 10°C without carbon dioxide with the exception of Frank Gollan (8) who uses a heart lung machine and then the picture changes

Horvath This is a particular species you are using?

Lewis These are mongrel dogs Adult dogs are those that have all of their permanent teeth and are probably over a year in age We differentiate between the old and the young because they responded differently to hypothermia

All of the ten adult dogs cooled with oxygen alone using a respiratory rate of 10 per minute fibrillated at temperatures between 19° and 23°C This is consistent with the results of many other investigators who have tried to cool dogs to temperatures below 20°C

Horvath What volume of ventilation was there?

Lewis We do not know the volume of ventilation but the pressure goes up to about 15 mm Hg during inspiration

Using 5 per cent carbon dioxide in oxygen eleven young dogs were cooled and to temperatures below 10°C without ventricular fibrillation In all of these eleven the heart continued to beat but none of them was successfully resuscitated Twelve adult dogs were also given 5 per cent carbon dioxide and oxygen Eleven of them fibrillated though at lower temperatures than was the case when oxygen alone was used In the twelfth dog the heart continued to beat down to a level below 10°C When we changed the technique and employed 10 per cent carbon dioxide and oxygen after the temperature had fallen to 30°C eleven adult dogs were cooled to temperatures below 10°C without fibrillation None of them however was successfully resuscitated

In rats and this has been true in Dr Andjus s experiments too one of the keys to successful resuscitation appears to involve the ability to obtain cardiac standstill rather than a continued heart beat at the very low temperatures We have achieved this in some dogs by another technique Thirty eight young dogs were cooled with 5 per cent carbon dioxide and oxygen until their temperature reached 20°C and then the carbon dioxide was discontinued and they were cooled further on oxygen alone In these experiments seventeen of the thirty eight went into cardiac standstill at an average temperature of 12 5°C They were kept at standstill from one half hour to an hour and a half and thirteen of them survived Eight of the thirty eight fibrillated and none of these survived Thirteen had a continued heartbeat down to temperatures below 10°C and only three of these survived

The blood pH values during these experiments are illustrated in Figure 129 If oxygen is used continuously while cooling these

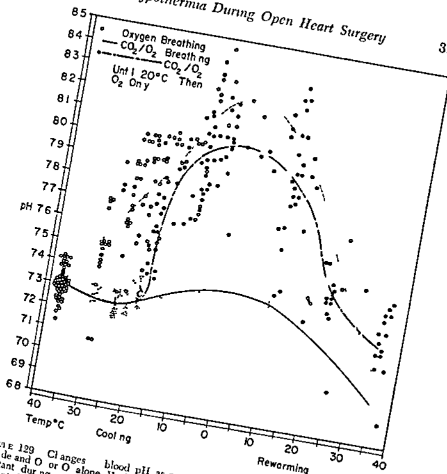


FIGURE 129 Changes in blood pH associated with respiratory mixtures of carbon dioxide and O_2 or O_2 alone With 5 per cent carbon dioxide the pH remains relatively constant during cooling but when O_2 alone is given the pH goes up rapidly (Reprinted by permission from Niazi S A and Lewis F J Profound hypothermia in the dog *Surg Gynec & Obst* 102 98 1956)

animals the pH rises in a striking fashion When carbon dioxide is used the pH remains at a relatively constant level slightly below normal

The pH changes for the animals in which the carbon dioxide was stopped at 20°C are shown as the middle curve in Figure 129 The pH remained relatively constant until the carbon dioxide was stopped at 20°C and then it shot up to high levels In earlier experiments done by Brown and Miller (9) a somewhat similar shift in pH at normal body temperature produced ventricular

fibrillation almost without exception, yet among our cold animals, 45 per cent went into standstill rather than fibrillation They used higher concentrations of carbon dioxide, however, and for a longer period than was the case in these *particular experiments*

The *plasma carbon* dioxide values, which are shown in Figures 130 and 131, change in a predictable manner In the *animals given* oxygen alone the carbon dioxide drops Given carbon dioxide and *oxygen, the plasma* carbon dioxide rises slightly

The only other blood chemical value we have much information on is serum potassium and in all the experiments, whether carbon dioxide was used or not, the potassium tended to drop during the

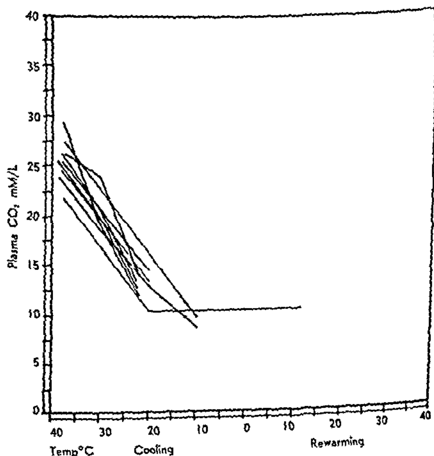


FIGURE 130 Plasma carbon dioxide in dogs during cooling when O_2 alone was given Reprinted, by permission from Niazi, S A, and Lewis, F J Profound hypothermia in the dog *Surg Gynec & Obst* 102, 98 (1956)

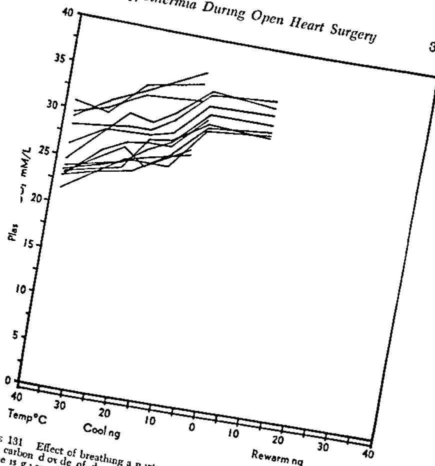


FIGURE 131 Effect of breathing a mixture of 5 per cent carbon dioxide in O_2 on the plasma carbon dioxide of dogs during hypothermia In contrast to the effect when O_2 alone is given the plasma carbon dioxide remains relatively constant Reprinted by permission from Niazi S A and Lewis F J Profound hypothermia in the dog *Surg Gynec & Obst* 102 98 (1956)

early part of cooling but to rise as the temperature fell below 20 C In the animals that recovered the potassium level dropped back to normal in the late rewarming period (Figures 132 and 133)

We will consider next the other type of experiment which suggests that the use of carbon dioxide may be helpful during profound hypothermia when operating on the heart at temperatures below 20 C As was mentioned we were unable to cool adult dogs much below 20 C without ventricular fibrillation Ten adult animals given just oxygen all fibrillated at temperatures between 19° and

use heavier doses of nembutal Thus the adult animals cooled to these low temperatures had between 55 and 75 mg of nembutal per kilogram of body weight a higher dose than is required in order to cool these animals without carbon dioxide We have not learned yet whether or not the deeper level of anesthesia was a factor in lowering the incidence of fibrillation though it may have been one

Behnke I think that one of the things to stress is the beneficial effect of carbon dioxide in high concentrations not only in promoting dissociation of oxygen from oxyhemoglobin but in lowering metabolic requirements Along this line I would like to point out the high survival particularly of brain tissue despite concentrations of inhaled carbon dioxide above 30 per cent In anesthetized cats respiration will come to a stop if the cat is allowed to re breathe an atmosphere to which sufficient oxygen is supplied With the concentration of carbon dioxide at about 30 per cent it is possible to produce anesthesia even with 20 per cent carbon dioxide The value of carbon dioxide in very high concentrations should be investigated further and I should like to ask Dr Andjus why he used carbon dioxide Did you have in mind a specific beneficial effect?

Andjus First of all I was not the first to use carbon dioxide as a cooling agent It was done by Dubois (10) some 60 years ago I knew that carbon dioxide depresses the heat regulation it suppresses shivering

I shall give some figures about the lethal concentrations of carbon dioxide According to Giaja and Markovic (11) 50 per cent carbon dioxide in oxygen is necessary to kill a rat at normal body temperature and it is only about 25 per cent carbon dioxide that is lethal for a cold rat of about 20°C So higher concentrations of carbon dioxide cannot be used without danger when dealing with hypothermic animals The toxicity of carbon dioxide increases with the fall of body temperature

In our experiments we used both progressive hypoxia and hypercapnia I have found that the oxygen consumption rate which is already reduced by low oxygen tension diminishes even more if carbon dioxide is added to the gas mixture

Montgomery What amount of carbon dioxide anesthetizes a rat in hypothermia? What carbon dioxide level at what body temperature?

Andjus I do not know that precisely The concentration should be smaller than at high body temperature, and it certainly depends on the level of hypothermia

Lewis An interesting difference between your experiments, Dr Andjus, and ours, of course has been the fact that we have not tried to asphyxiate our animals We have used artificial respiration and oxygen all through cooling — until the period of cardiac stand still

Andjus That is very interesting in connection with the length of time during which you are able to keep your animals at very low temperatures with subsequent recovery because as I showed previously, I was not able to keep them more than 1 hour in suspended animation at 0 degrees with a subsequent 100 per cent recovery Your animals, however revived even after 3 hours This is perhaps because of the amount of oxygen present in the blood in the last stage of cooling

Lewis It may be In our last experiment twenty four rats with incers all had cardiac standstill for 2½ hours at 0 degrees

Andjus But perhaps they were full of oxygen This is a very ...eresting point that should be investigated Perhaps by giving oxygen through the alimentary canal you will be able to keep the animal a longer time at 0 degrees or below with the possibility of reanimation It would be enough perhaps to keep these cold animals, with arrested hearts at a high oxygen pressure just to secure oxygenation by diffusion

Lewis To return to the matter of using carbon dioxide there has been some reservation in our minds concerning its relative importance during hypothermia We may not know just what all its effects are as Captain Behnke has pointed out but one effect that seems to be quite definite is a better control of the blood pH level The pH remains at a relatively constant level when carbon dioxide is employed

In any case, after the experiments I have described we felt the use of carbon dioxide in humans was justified Among the first thirty-one patients on whom we did open heart operations during hypothermia we had eleven cases of ventricular fibrillation In these a standard anesthesia machine was used employing oxygen and with an anesthetist pumping the bag This is apt to result in changes of carbon dioxide and pH at normal temperatures and I think that these changes are probably a good deal more dangerous at low temperatures We only have pH measurement in thirteen

of these patients and in some of them an effort had been made, using a mass spectrometer to keep the alveolar carbon dioxide at a relatively constant level but nonetheless in ten of these thirteen the pH rose above 7 45 when the temperature of the patient was below 30°C Five of these ten had ventricular fibrillation The three in whom the pH stayed below 7 45 did not fibrillate In three of the ten patients with high pH levels the pH rose above 7 6 and all three of them had ventricular fibrillation

We have used 5 per cent carbon dioxide in oxygen in fifteen patients undergoing open heart surgery during hypothermia Only one fibrillated This was a 54 year old man who had coronary arteriosclerosis as well as pulmonary hypertension and an atrial septal defect There has been a lower incidence of fibrillation since we have used carbon dioxide but our skill I suppose was greater too in these last operations It is hard to reach many conclusions but the clinical results suggest that the change in technique has been worth while

The studies in deep hypothermia with rats and dogs led us to see if deep hypothermia could be achieved in primates too so we tried monkeys So far we have only cooled five monkeys to a state of cardiac and respiratory standstill at temperatures below 10°C but we were gratified to find that it was simpler to cool monkeys than it was to cool dogs Four of the first five monkeys survived with periods of cardiac standstill from 30 to 56 minutes in duration with no evident damage These four monkeys are shown in Figure 134

The respiratory gas has been 5 per cent carbon dioxide and oxygen throughout We did not have to shift to oxygen at 20°C in order to achieve standstill as was the case in dogs

[Presentation of motion picture with the following comments by Dr Lewis]

Sweet You stopped the ventilation on the monkeys when the heart stopped?

Lewis Yes One monkey was respired from the start at a rate of 10 per minute His temperature was 35 5°C when he was anesthetized and intubated and the cooling was started

The pulse rate was about 180 a minute to begin with By the time the temperature had fallen to 25°C there was already quite a striking reduction in pulse rate with lengthening of the cardiac



r 134 These four monkeys all survived body cooling to temperatures bel
with periods of cardiac standstill that lasted from 30 to 56 m s

systole and rather profound changes in the T waves which always occur at these temperature levels

The temperature of the monkey when cardiac standstill occurred was 14°C Five minutes after the heartbeat had stopped we stopped the respirator When we were ready to rewarm him we hooked the respirator back up and warmed the chest with hot water After a period of standstill which lasted 56 minutes the heart started to beat again At its low point this animal's temperature was 9 5 C The lowest temperature we have achieved in the monkeys was 4 5°C To get lower rapid cooling once the heart stopped would be required

When the body temperature had returned to 35 C the pulse rate was back up to from 175 to 180 About 10 minutes after his temperature had reached 35 C he was taken off the respirator and he was reacting sluggishly to stimuli Twenty four hours after cooling he appeared normal The other monkeys that have survived also appear normal in every respect

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CEREBRAL STUDIES DURING LOCAL AND GENERAL HYPOTHERMIA

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PROCEEDING FROM ALL THE ENCOURAGEMENT that the cardiac surgeons, especially Dr Bigelow, gave us, we were anxious to find out if, indeed, the cerebral metabolic rate would be reduced satisfactorily in this condition of lowered body temperature Our first efforts in this field were to measure the cerebral oxygen consumption This work was begun when, following Lougheed's efforts, we decided we could not successfully and conveniently set up apparatus to perfuse the animal's brain from an extracorporeal pump

We first thought, too that we would use only cooled blood from the animal itself The arterial blood from one carotid artery was diverted through a cooling apparatus and a pump and returned to the distal end of that carotid while the other trunk arteries to this animal's brain were occluded This preparation in the hands of Dr Lougheed and Dr Kahn (1), proved to be just as susceptible to ventricular fibrillation as any others that had been set up by other experimenters Though the torso as judged by the rectal temperature, was cooled only to 35°C by the cold blood returning to the heart from the brain, nevertheless, five out of six of these dogs went into ventricular fibrillation We thought that this probably could be correlated with the previous work of Hoff and Stansfield (2) who found that cooling of one portion of the ventricle predisposes to fibrillation of that structure following a single shock applied anywhere in the noncooled portion of the ventricle

Lewis Were these dogs hyperventilated without carbon dioxide?

Sweet These dogs were ventilated without added carbon dioxide in this study I do not think Lougheed and Kahn hyperventilated them At any rate this preparation did permit one to control the amount of blood that was being circulated into the dog's brain so that by measuring the cerebral arterial venous oxygen differ

ences and taking the figure for the rate of perfusion we could emerge with an accurate estimate of the cerebral metabolic rate of the dogs Thus we did get this crucial information from them even though we also found out that this did not seem to be a very safe way to cool the dogs brain

These cerebral metabolic rates for dogs cooled to temperatures of the order of 25°C ran from 23 up to 35 per cent of the normal of the order of a quarter to a third of the normal metabolic rate This incidentally was about parallel to the drop in total body oxygen consumption at this temperature With this information then we felt that if we cooled our patients to this level we could effectively occlude the cerebral circulation for at least three times as long as we could with them at body temperatures

We also got further useful information from the animals whose brains were cooled by perfusion of cold blood namely that with an electroencephalographic tracing in progress throughout this period we acquired a good idea of the degree of normality of cerebral function or at least of the electrical signs thereof We found as others had found that in the hypothermic state the potentials in the electroencephalogram were generally reduced with a greater prominence of the slow waves With further depth of the hypothermia dropping out of these slow waves is succeeded by electrical silence

Fremont Smith At what temperature did you get the silence?

Sweet These dogs were not cooled to low enough levels to flatten the EEG to a straight line by virtue of the hypothermia alone Electrical silence tended to appear at about 20°C in the monkeys of Callaghan McQueen Scott and Bigelow (3)

Fremont Smith Did you try any buried electrodes or only surface electrodes?

Sweet Cerebral temperature was recorded from a thermocouple buried in the cerebral hemisphere but the electroencephalogram was obtained from a pair of electrodes resting only on the external surface of the dura mater

Fremont Smith No deep ones?

Sweet Not on the brain

Fremont Smith I meant down in the thalamus or lower

Sweet No we do not have any data from depth electrodes for EEG recording within the brain

Sweet At any rate we hoped that the brain waves would be a reliable early indicator of cerebral anoxia in the hypothermic state Such anoxia at normal temperatures increases the number of slow waves and reduces the general amplitude of the tracing One other test of the safeguarding effect of the hypothermia was obtained by this kind of maneuver, once the dog was cooled down into the low 20s, he was then changed from his ventilation with room air to ventilation with 100 per cent nitrogen Eight dogs were ventilated in this fashion for from 15 to 30 minutes All but one made a complete recovery without clinical evidence of any neurological deficit from the anoxia when they were at these low temperatures Actually, the ECG usually showed marked abnormality before EEG changes were striking The one animal with a gross abnormality in the EEG after hyperventilation with 100 per cent nitrogen did have a clinical neurological deficit upon rewarming Since that animal had lost over half his blood volume the hypothermic state had in that case a prejudiced chance to demonstrate its value But this experience did suggest that grossly abnormal brain waves constitute an indication to restore the cerebral circulation to normal

Montgomery How long can the normothermic dog breathe 100 per cent nitrogen and make a complete recovery?

Sweet No dog was ventilated on pure nitrogen at normal temperatures This was a device which we used in an effort to provoke complete anoxia as rapidly as we could in preference to say, shutting off the blood supply It proved exceedingly difficult to occlude the blood supply completely to the dog's brain because there will always be some going up along the anterior spinal artery and this is hardly a feasible structure to occlude

Montgomery Would you expect at normal temperature that damage would occur after 3 minutes of nitrogen inhalation?

Sweet Weinberger Gibbon and Gibbon (6) have demonstrated that 3½ minutes of complete vascular occlusion to the brain in the cat is the limit beyond which the animal will not fully recover

Horvath With 100 per cent nitrogen it is 90 seconds

Sweet That incidentally, demonstrates the point that the nitrogen inhalation is a more critical test because it actually washes out the oxygen that is already there and also deprives the individual of fresh oxygen

Montgomery And that produces some permanent damage not just transient?

Horvath Permanent damage with dogs at 90 seconds, but *transient damage with man*, in roughly a minute or a minute and a half

Sweet This is all the more encouraging to me because we were taking a 3 minute figure as the safe maximum for complete anoxia in the normothermic state (6) As I said, the period of toleration of such hyperventilation with nitrogen is from 15 to 30 minutes in the dog at about 25°C or ten to twenty times as long as the period tolerated by the dog at normal temperature, according to Dr Horvath's statement

At the same time that Lougheed and Kahn were doing this work in our laboratory, Rosomoff and Holaday (7) in New York were *also measuring* cerebral oxygen consumption by putting a flow meter into the arterial input to their dogs' brains They emerged with similar results, namely that at 26°C ¼ to ½ as much oxygen was consumed as at 35°C We heard Dr Shumacker *tell* us that in four individuals in whom cerebral blood flow measurements have been carried out in man at low temperatures, a similar reduction in cerebral oxygen consumption is achieved

Actually we have a very much simpler task neurosurgically than the cardiac surgeon has We are not going to operate on the heart at least we are hoping not to have to, so that the direct stimulus to this structure to initiate ventricular fibrillation will be absent Furthermore the arrest of circulation we wish to achieve in order to operate on an exceedingly vascular lesion within the depths of the brain is so readily carried out, involving as it does only occlusion of two carotid and two vertebral arteries in the neck, that it is not a one time matter as it is with the cardiac surgeon His complex careful maneuvers to achieve a dry intracardiac field and then restore the circulation virtually preclude his doing this more than once during an operation

In our patients [illegible] as many times as we like [illegible] *that the* cardiac surgeon does not have, [illegible] blood flow to this area a bit we can let the arteries bleed out into the field and not lose a dangerous *amount of blood*

The principal reason we need a dry field or a field that is nearly dry is that we must handle the structures adjoining our lesion with the utmost care If we try to suck away *the blood as rapidly as* it comes into the field from a highly vascular lesion, we are liable to suck away a bit of the nervous structure as well and cause the

death of the patient, so that our need for a dry field is of a substantially different nature from that of the cardiac surgeon. In line, then, with these needs, the first case that we did, a massive arteriovenous malformation lying just above the thalamus in the mid brain, was a patient in whom we were able to occlude both carotids and both vertebral arteries for a total of 47 minutes. This 47-minute occlusion was spread through seven different intervals over the course of 2 hours. This young man woke up from this procedure and, in the limited appraisal that we were able to make of him in the 5 days that he survived, we thought that his mental status might well have been normal or recovered to normal.

He died of something that we had not anticipated at all. We had thought that we might be troubled in these patients with postoperative hemorrhage because of the prolonged bleeding and clotting time known to accompany the hypothermic state, but this young man developed a thrombosis at the site of one of our occluding points on one vertebral artery. This thrombus slowly propagated, or so we assume, up alongside his brain stem, and at the time that the thrombosis extended into the vertebral artery up near its junction with the basilar artery he developed rather rapidly respiratory difficulties and died when there could no longer be a retrograde flow from the basilar or other vertebral artery.

Since that time, we have come across the work of two Swedish investigators, Gelin and Lofstrom (8), who found clumping of erythrocytes in the hypothermic state, the same sort of thing, they say, that Knisely (9) showed in traumatic shock.

Fremont-Smith: Sludging.

Sweet: Yes, he called it sludging. This has naturally been a source of major concern to us because in the relatively much smaller vessels with which we are working, thrombosis is a major problem with us, anyway, when we do any work on any of the cerebral trunk arteries. One thing that we have since done is to make our occlusions in an exceedingly gentle fashion and now instead of using rubber-shod clamps on the two smaller vessels, the two vertebral arteries, we occlude by pressing them gently against the bone on which they lie. Even the occlusion of all four of the trunk arteries in man may not produce a completely dry field in the brain, but we can control the little hemorrhage remaining in the field satisfactorily.

I am anxious to get some help on a number of points here. In one of our cases, just after we transferred the man from a bath tub

filled with icewater to the operating table, his electrocardiogram showed alarming changes

These consisted of enormous high voltage waves, nearly twice as high as the ordinary QRS complex, and spread out over an interval of about three to five times the width of the ordinary QRS complex, we had never seen anything like this before, and in fact, the electrocardiographers in Dr Paul White's laboratory had not either They were at first inclined to call this auricular flutter Subsequently, Goldberg,* working in the Laboratory of Anesthesiology at the Massachusetts General Hospital has found that a number of hypothermic dogs, some minutes before they have gone into ventricular fibrillation have shown this kind of electrocardiographic change He interpreted this as the exaggerated appearance of a right bundle branch block It is an ominous high voltage wave that looks in the electroencephalogram, a little like a δ wave with notches on it

Lewis I think that ventricular extra systoles or ventricular tachycardia predispose to ventricular fibrillation Sometimes the complexes are quite wide during hypothermia You do not think these were just ventricular extra systoles?

Sweet They were so wide they were thought not to be, but at any rate I had better mention what was done about this Relying on data obtained by Bigelow, Lindsay, and Greenwood (10) that show there is often an increased venous pressure in the right atrium in the hypothermic state just before ventricular fibrillation sets in we rapidly withdrew 50 ml of blood from a catheter leading to the right atrium The electrocardiogram settled back to a much more normal looking configuration Happily, the catheter had been placed previously to permit drawing of systemic venous blood samples

I do not know whether or not there is any cause and effect relationship here between the venesection and the recovery of the ECG Have you ever tried this Bigelow maneuver of withdrawing blood rapidly from one of the major systemic veins entering the heart?

Lewis No we have never tried that We have seen abnormal ECG patterns while we moved our patients but I think that this is usually caused by electrical interference, that is, I do not think the abnormal ECG pattern represents the heartbeat

*Goldberg L Personal communication

Ferrer Dr Sweet, what was the rate of impulse formation of these large complexes you have mentioned?

Sweet Fairly rapid Of the order of 180

Ferrer We have seen a similar phenomenon in the noncooled cardiac subject undergoing mitral surgery The rate, however, was not rapid and usually was less than 100 Three of them, in whom the end result was always cardiac arrest, developed this ventricular pacemaker during the operation and presumably as the metabolism of the heart changed, the complexes got smaller in voltage and slower in rate of formation until there was cardiac arrest This, again, is not the cooled subject but one at an ordinary body temperature We regard these ECG findings as a grave prognostic sign indicating the possibility of imminent cardiac arrest

Lewis Is this a ventricular paroxysmal tachycardia?

Ferrer It is certainly a ventricular arrhythmia Since tachycardia technically is any rate above 100 we hesitate to use that word but it seems to us it was a ventricular rhythm which existed without there being any electrical evidence of atrial activity present at the same time, and which gradually slowed It was not chaotic enough in form to be given the term irregular slow ventricular fibrillation "

Horvath It doesn't look like ventricular block?

Ferrer This possibility has been suggested to us but in the absence of a P wave before each QRS complex this intraventricular block cannot be diagnosed and actually I doubt this was the explanation The T waves are fairly large along with this large QRS voltage and the voltage of both complexes decreased *pari passu*

Talbott Dr Sweet what was the temperature of the patient when this occurred?

Sweet It was 29 4°C

Talbott The patient was on the way down or stable?

Sweet The patient was on the way down This incidentally, was not an artifact of movement because it was recorded when he was lying on the operating table just after he had been transferred

Horvath These are only occurring occasionally? They are not definite runs of, say ten or fifteen beats or better?

Sweet I cannot tell you how many there were but this went on for the order of a minute

Horvath That is quite a usual finding in hypothermic animals if they are on their own respiration You get these occasional bursts of activity which are of ventricular origin which disappear and which very frequently are accompanied by succeeding cardiac arrest They will start somewhere around 30°C but may not be seen on the other hand until the animal is down in the low 20s This is not a very unusual finding in animals on their own respiration so far as cardiac pattern is concerned (11)

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Horvath I think so I do not think they are indicative of anything nice going on but they may not go into fibrillation they may not go into cardiac arrest and sometimes they clear up completely but their very presence is an indication that something is wrong

Behnke Are you working around the carotid sinus when you occlude the vessel?

Sweet The occlusion is done lower down in the neck

Behnke If a deep sea diver may make a suggestion to a neurosurgeon during the war we were interested in the period of useful consciousness using Rosen s pressure cuff to occlude the blood supply This was accomplished by raising the pressure abruptly by means of a pressure reservoir in a sphygmomanometer pressure cuff wrapped around the neck The period of useful consciousness was about 10 seconds at atmospheric pressure At high altitudes this time period could be reduced to 7 seconds I think it was a very effective way of occluding the blood supply without any obstruction of respiration because we could count until unconsciousness supervened In only one of our group was consciousness maintained despite apparent shutting off of blood supply

Sweet That is a magnificent suggestion It is a little difficult to dissect out the vertebral arteries and if they could be occluded by your method time would be saved and there would perhaps be less danger of late thrombosis However the fact that you lost consciousness does not prove that the cuff effectively occluded the vertebral arteries because we have produced unconsciousness in several patients upon occlusion only of both common carotid arteries

Burton But you have to put in cooling blood

Sweet We occluded only when we want to cut off the circulation to work on the arterial lesion We have had the brain all cooled off for some time

Burton Have you tried on dogs to see whether you didn't decrease the incidence of ventricular fibrillation by cooling the brain specifically but supplying a considerable amount of heat to the rest of the body to compensate so there wasn't any drop of heart temperature? Is this feasible?

Sweet I wonder if it may not be I see that Jensen and Parkins (12) have reported on differential cooling of the brain by cooling the blood flowing into one carotid They achieved a low incidence of spontaneous cardiac arrhythmia In the single paragraph that is given in the *Federation Proceedings* no details of the technique are given

Horvath They fibrillate but not very frequently Instead of 50 per cent fibrillation they have 25 per cent

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Horvath By that procedure you have cooled the brain down very rapidly and sometimes so quickly that you really do not realize that the brain temperature is down in the neighborhood of 7° or 8°C It is a very rapid method of cooling if you have a small mass to cool It is not easy to control

Sweet There is another subject worth alluding to There is some evidence that in the hypothermic state perhaps the major outstanding problem for an intracranial surgeon can be usefully dealt with namely the ischemia and edema in the post traumatic or postoperative period

There is one spectacular report from Liverpool by Sedzimir Jacobs and Dundee (13) of a patient in whom proximal occlusion of the middle cerebral artery was employed in the hypothermic state to stop bleeding from a middle cerebral aneurysm A useful degree of function of the contralateral arm was the surprising finding immediately after the patient had awakened following the operation The patient then on three successive occasions went back into a state when she was essentially at death's door with an enormous respiratory rate high temperature deep coma and

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dilated, fixed pupil on the side of the ischemia and hemorrhage. She was brought out of each of these moribund episodes by protracted periods of hypothermia, but she died later. Rosomoff (14) has also shown that if the dog's middle cerebral artery is divided when the animal is at 25°C, cerebral infarction is prevented or is greatly diminished as compared to that found in control normothermic dogs subjected to the same operation

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APPENDIX: AUTOBIOGRAPHICAL SKETCHES OF PARTICIPANTS

AUDREY SMITH I work with Dr A S Parkes, F R S, in the Department of Experimental Biology at The National Institute for Medical Research in London, and my field is low-temperature biology In 1945 Dr Parkes who was interested in reproductive physiology, started a program of work on the effects of chemical and physical agents on the gametes Among other physical agents, he was interested in the effects of intense cold He was intrigued by the idea that if a cell could be cooled to a very low temperature, the temperature for instance, at which atmospheric gases are liquid, all metabolic processes would be brought to a standstill However long the cell was kept at that temperature, it would therefore not age, and providing it could be thawed without damage, it would show no signs of deterioration centuries later Previous experiments by other groups of workers including Luyet and Hodapp (1), Shettles (2), and Jahnel (3) suggested that it should be possible to preserve spermatozoa in this way Dr Parkes followed up their work and found that when ampules or test tubes of human semen were frozen in liquid air or in solid CO_2 and thawed out hours, weeks, or months later, a small proportion of the human spermatozoa survived and were actively motile apparently healthy (4) He was unable to obtain similar results using the spermatozoa of any other mammalian species and the work was put aside until, in 1948, we were joined at the National Institute by Mr Christopher Polge His project was to develop artificial insemination in poultry

Dr Parkes suggested that we should try preserving the semen at very low temperatures, using a concentrated fructose solution as the semen diluent, because this had previously been used by Shaffner Henderson, and Card (5), who had obtained promising results

In our hands however treating the sperm with fructose and freezing quickly or slowly to −79°C or −190°C resulted in its complete destruction, as we were able to

show by studying both the motility and stained smears

Some months later we repeated the experiments but by mistake we used as the semen diluent a solution containing 10 per cent glycerol instead of the solution of fructose

In this way we discovered accidentally that glycerol had the remarkable property of protecting avian spermatozoa from the otherwise damaging effects of freezing to storage at and thawing from very low temperatures (6) Later glycerol was found to have a similar action in protecting mamalian cells

Since then Dr Parkes my colleagues and I have done a considerable amount of work on preservation of mammalian spermatozoa red blood cells endocrine and other tissues at very low temperatures and in media containing glycerol We tested their variability by *in vitro* tests and by reintroduction into the animal body (7 8) We went on to see whether whole organs from mammals could stand preservation in this way

The first organ so tested was the guinea pig uterus which had been treated with glycerol and preserved at 79°F In the presence of glycerol we found it would resume contractions *in vitro* and responded normally to drugs It also showed immunological reactions

No attempts were made to freeze whole animals until 1954 by which time we had been joined by Dr Andjus from Belgrade

R K ANDJUS I am a Doctor of Science not of medicine I am assistant professor of Physiology at the University of Belgrade where I teach Physiology in the Faculty of Science

As far as my research work is concerned and especially for the last 7 years I have been interested in hypothermia with the possibility of resuscitating nonhibernating homoiothermic animals after lowering their body temperature to zero and below the freezing point

I had the privilege of working under Professor J Giaja who is a leading physiologist in my country and also is in the Faculty of Science Prof Giaja's main interest is in thermoregulation and for many years before the war he was interested in hypothermia Later I had the privi

lege of working for one year under Dr A S Parkes at The National Institute for Medical Research in London, with Dr Audrey Smith and Dr J Lovelock

This is how I started to work on hypothermia While learning to perform an hypophysectomy in rats, I found some of my rats died of asphyxia during the operation because the trachea had to be occluded from time to time I knew that my professor used to cool rats, in 1940, by exposing them to low barometric pressure He also found their oxygen consumption at 15°C was very low So I thought if I performed my hypophysectomies in cooled rats they would tolerate hypoxia This expectation proved correct

I would like to tell you something about how I started to work on resuscitating animals Since my faculty as well as the library were completely burned out during the last days of the war so that literature was not easily available I did not know that during the war the Germans had investigated different reanimation procedures in cooled animals and human beings and that they insisted on rapid rewarming of the whole body as the only effective means of reanimation I thought that warming the whole body of an animal with an arrested heart meant that the metabolism of the tissues would be raised before an adequate circulation was re-established I thought that perhaps it would be possible to reanimate an animal by heating the heart locally thus re establishing the circulation first, so I started with experiments on rats and tried to apply heat locally to the heart by applying a metal spatula which had been heated on a Bunsen flame to the chest of the cold animal It worked and that is how I started investigating suspended animation and resuscitation of animals from zero

PETER C. KRONFELD I am an ophthalmologist, and my field is aqueous humor dynamics to the extent to which they can be studied in the living human eye You and I have at least one little field in common and that is experimental cataracts caused by various forms of insult I am very much interested in the type of lens opacities that occur in animals that have been resuscitated after prolonged and

severe states of hypothermia such as those which will be discussed at this meeting

F A SIMEONE I am a surgeon and am Professor of Surgery at Western Reserve University and Director of Surgery at City Hospital of Cleveland Ohio at the present time

I first became interested in cold injury when I was a student in high school and read Xenophon s account of the dreadful sufferings from cold injury that Darius s army underwent *when they moved across Asia Minor*

During World War II I had the opportunity to study soldiers who developed cold injury during the campaigns in the *Mediterranean Theater of War I wrote the history* of cold injury for that Theater* and collaborated with Dr Michael E DeBakey (of the Department of Surgery at the Baylor University School of Medicine Houston Texas) in the preparation of the volume on cold injury for the Army s *Surgery in World War II* (9) Since the war I have participated in a collaborative project to study in follow up a sample of veterans who had incurred cold injury during World War II The data have been collected but their interpretation has not yet been com pleted

WILLIAM H SWEET My interest is a very much more recent one in this subject than that of most of you and it began when Dr Lougheed (10) from the University of Toronto who now works in Dr H Botterell s Department of Neuro surgery at that university came to spend a year with us to do investigative work We were both very discouraged about our capacity to handle vascular disorders afflicting the brain one of the principal problems being to supply blood or oxygen to this brain from some source while we cut off the blood supply in the main trunk vessels.

Dr Lougheed spent most of his projected year with me seeking by various technical maneuvers to supply blood to the brain by shunts of one sort or another and only near the end of this year did we finally give up these methods and decide to try the crude procedure of actually cooling the whole animal to decrease its cerebral oxygen requirement in that fashion However this turned out to

*Simeone F A Report to the Surgeon MTOUSA on Trench Foot in the Italian Campaign 1945

be far less crude and lacking in feasibility than expected and we both have become quite enthusiastic about it.

RICHARD SCHATZKI: I am a clinical radiologist. At the conclusion of the formal studies of the frostbite cases in the Korean conflict, Colonel Blair, Dr. Talbott and other members of the Cold Injury Commission had a series of roentgenograms, excellent follow up studies of some sixty or seventy of the soldiers who had suffered frostbite in Korea. I was asked to undertake a study and interpretation of these roentgenograms. I have been engaged in this study for about 3 years now.

FREDERICK A. FUHRMAN: I became interested in cold in 1941. I was converted from a pharmacologist to a physiologist when I went to Stanford University to work with Dr. John Field. We were studying the effect of temperature on the metabolism of mammalian tissues, and this naturally led to other problems related to cold, in particular to one on cold injury itself. This work was done with Dr. Crismon during the war.

I then became interested in hypothermia and other aspects of cold, especially the effect of drugs in hypothermic animals, and now I have gone back to some of the fundamental problems relating to frostbite again.

…LAND E. HEDBLOM: At the present time I am the Medical Officer of Task Force 43, Operation Deep Freeze, on which expedition I will depart very soon for New Zealand and then Antarctica.

HUGH MONTGOMERY: I do not know when my interest in the effect of cold on tissues began unless it was years ago while I was gathering material for lectures on temperature regulation, or when I was in the Navy early in the war and seeing a few patients with cold injuries, or perhaps it was when I was in the Pacific Area taking care of a large number of injuries ranging from burns to warm sea immersion effects. After returning to the University of Pennsylvania at the end of the war, while searching for interesting physiological tools, Dr. F. C. Dohan told me that Dr. P. W. Davies and Dr. F. Brink, Jr. (11) in the Johnson Foundation had improved a platinum electrode for measurement of oxygen in solutions and had carried it to the

point of using it upon the surface of the cat's brain It seemed that with our particular *interest in the peripheral* vascular field we might obtain some information on oxygen in the skin of normal and ischemic extremities

After obtaining some semi quantitative measurements of oxygen tension in normal human skin, we followed the changes in oxygen tension in skin resulting from induced changes in blood flow Here the effect of heat and cold came into prominence Soon we were exposing skin directly to as hot water as we could stand, and to ice *water* We were *interested in measuring the low* oxygen tension that resulted when the skin was *immersed in* cold water and the high levels of oxygen that *resulted in* cold skin from breathing oxygen These latter were higher levels than were found in the skin unexposed to cold

I then knew that the concept that damage by cold may be a result of anoxia was open to investigation and we carried out experiments on the skin of our feet and on the muscle and subcutaneous spaces *of the legs of* rabbits We were *able to demonstrate that cold does lower the* oxygen tension of these tissues, and that inhalation of oxygen *during the same period* early during what we might call immersion foot, raises that oxygen tension at least to a pre immersion level But the increase in tissue oxygen was only a slight protection against the damage caused by this degree of cold so I think it is fair to say that anoxia is not the major cause of immersion foot Having become absorbed in this problem we have gone on to study *effects of cold short of freezing*

J PETER KULKA While studying the pathology of rheumatic disease I began to wonder if some of the injury in rheumatic granulomatous lesions might be the result of circulatory insufficiency *I then started to look into the tissue changes* produced by various agents which could impair the circulation *one such agent is cold*

I had little opportunity to pursue this subject further until *I was called to active* duty in the U S Army and received a part time assignment, as pathologist *to Colonel* Blair's research project on cold injury at Harvard Medical School

Since then I have become more and more interested in cold induced lesions because they represent an inflammatory process in which the intensity and duration of exposure to the etiologic agent may be controlled and a relatively subtle initial physicochemical change results in a chain reaction which may lead to extensive tissue death

We are currently extending the project started by Colonel Blair with emphasis on the pathogenesis of local cold injury

JOHN LEWIS Despite the fact that I come from one of the coldest parts of the country I have never been seriously frost bitten so it may be a little difficult to understand why I have studied hypothermia As a matter of fact I was trained primarily as a gastrointestinal surgeon but in that particular field my own professor offered such a tremendous amount of competition that I felt I had to search for different fields of investigation

I worked on a trench foot study group for a few months during World War II and then after the war I investigated regional hypothermia for a short period of time but became disappointed in it Then following the publications of Bigelow in 1950 (12) in which he suggested that total body hypothermia might be a way of doing heart surgery I started investigating problems of total body cooling Since then we have cooled animals successfully even to temperature levels as low as 0°C I hope that during the conference I will have the opportunity to ask about some of the problems we have encountered in doing this type of cooling

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